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**SUPPLEMENTARY MATERIALS**

# Genome-wide association analyses identify multiple loci associated with central corneal thickness and keratoconus

Yi Lu[1]*, Veronique Vitart[2]*, Kathryn P Burdon[3]*, Chiea Chuen Khor[4-7]*, Yelena Bykhovskaya[8], Alireza Mirshahi[9], Alex W Hewitt[10,11] , Demelza Koehn[12], Pirro G Hysi[13], Wishal D Ramdas[14,15], Tanja Zeller[16], Eranga N. Vithana[4,5], Belinda K. Cornes[4], Wan-Ting Tay[4], E. Shyong Tai[6,17], Ching-Yu Cheng[4-6,18], Jianjun Liu[6,7], Jia-Nee Foo[7], Seang Mei Saw[6], Gudmar Thorleifsson[19], Kari Stefansson[19,20], David P Dimasi[3], Richard A Mills[3], Jenny Mountain[21,22], Wei Ang[22], René Hoehn[9], Virginie J.M. Verhoeven[14,15], Franz Grus[9], Roger Wolfs[14,15], Raphaële Castagne[23], Karl J. Lackner[24], Henriet Springelkamp[14,15], Jian Yang[25], Fridbert Jonasson[20,26], Dexter YL Leung[27], Li J Chen[27], Clement CY Tham[27], Igor Rudan[28,29], Zoran Vatavuk[30], Caroline Hayward[2], Jane Gibson[31], Angela J Cree[32], Alex MacLeod[33], Sarah Ennis[31], Ozren Polasek[29,34] , Harry Campbell[28], James F Wilson[28], Ananth C Viswanathan[35], Brian Fleck[36], Xiaohui Li[37], David Siscovick[38], Kent D. Taylor[37], Jerome I. Rotter [37], Seyhan Yazar[11], Megan Ulmer[39], Jun Li[40], Brian L. Yaspan[41], Ayse B. Ozel[40], Julia E. Richards[42], Sayoko E. Moroi[42], Jonathan L. Haines[41], Jae H. Kang[43], Louis R. Pasquale[43,44], R. Rand Allingham[45], Allison Ashley-Koch[39], NEIGHBOR consortium[46], Paul Mitchell[47], Jie Jin Wang[47], Alan Wright[2], Craig Pennell[22], Timothy D Spector[13], Terri L Young[48], Caroline CW Klaver[14,15], Nicholas G Martin[1], Grant W Montgomery[1], Michael G Anderson[12,49], Tin Aung[4,5,50], Colin E. Willoughby[51], Janey L Wiggs[44]*, Chi P Pang[27]*, Unnur Thorsteinsdottir[19,20]*, Andrew J Lotery[32,33]*, Christopher J Hammond[13]*, Cornelia M van Duijn[14,15]*, Michael A Hauser[39]*, Yaron S Rabinowitz[8,52]*, Norbert Pfeiffer[9]*, David A Mackey[10,11]*, Jamie E Craig[3]*, Stuart Macgregor[1]*, Tien Y. Wong[4-6]*

*These authors contributed equally.

1. Queensland Institute of Medical Research, Brisbane, Queensland,Australia.
2. MRC Human Genetics Unit, Institute of Genetics and Molecular Medicine, Edinburgh, UK.
3. Department of Ophthalmology, Flinders University, Flinders Medical Centre, Adelaide, South Australia, Australia.
4. Singapore Eye Research Institute, Singapore, Singapore.
5. Department of Ophthalmology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore.
6. Saw Swee Hock School of Public Health, National University of Singapore.
7. Human Genetics, Genome Institute of Singapore, A*STAR, Singapore.
8. Regenerative Medicine Institute, Ophthalmology Research, Department of Surgery, Division of Surgical Research, Cedars-Sinai Medical Center, Los Angeles, CA, USA.
9. Department of Ophthalmology, University Medical Center Mainz, Mainz, Germany.
10. Centre for Eye Research Australia, University of Melbourne, Royal Victorian Eye and Ear Hospital, Melbourne, Australia.
11. Lions Eye Institute, University of Western Australia, Centre for Ophthalmology and Visual Science, Perth, Australia.

12. Departments of Molecular Physiology and Biophysics, University of Iowa, Iowa City, Iowa, USA.
13. Department of Twin Research and Genetic Epidemiology, King's College London School of Medicine, St Thomas' Hospital, London, United Kingdom.
14. Department of Ophthalmology, Erasmus Medical Center, Rotterdam, The Netherlands.
15. Department of Epidemiology, Erasmus Medical Center, Rotterdam, The Netherlands.
16. University Heart Center Hamburg, Clinic for General and Interventional Cardiology, Hamburg, Germany.
17. Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore.
18. Centre for Quantitative Medicine, Office of Clinical Sciences, Duke-NUS Graduate Medical School, Singapore.
19. deCODE genetics, 101 Reykjavik, Iceland.
20. Faculty of Medicine, University of Iceland, 101 Reykjavik, Iceland.
21. Telethon Institute for Child Health Research, Centre for Child Health Research, University of Western Australia.
22. School of Women's and Infants' Health, University of Western Australia, Perth 6009, Australia.
23. INSERM UMRS 937, Pierre and Marie Curie University and Medical School, Paris, France.
24. Clinical Chemistry and Laboratory Medicine, University Medical Center Mainz, German.
25. The university of Queensland, Brisbane, Queensland, Australia.
26. Department of Ophthalmology, Landspitali National University Hospital, Reykjavik, Iceland
27. Department of Ophthalmology & Visual Sciences, The Chinese University of Hong Kong, Hong Kong Eye Hospital, 147K Argyle Street, Kowloon, Hong Kong.
28. Centre for Population Health Sciences, University of Edinburgh, Edinburgh, UK.
29. Croatian Centre for Global Health, University of Split Medical School, Croatia.
30. Department of Ophthalmology, Hospital 'Sestre Milosrdnice', Zagreb, Croatia.
31. Genetic Epidemiology and Genomic Informatics Group, Human Genetics, Faculty of Medicine, University of Southampton, Southampton General Hospital, Southampton, UK.
32. Clinical Neurosciences Research Grouping, Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton, Southampton General Hospital, Southampton, UK.
33. Southampton Eye Unit, Southampton General Hospital, Southampton, UK.
34. Department of Public Health, University of Split, Croatia.
35. NIHR Biomedical Research Centre for Ophthalmology, Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology, London, UK.
36. Princess Alexandra Eye Pavilion, Edinburgh, UK.
37. Medical Genetics Institute, Cedars-Sinai Medical Center, Los Angeles, CA, USA
38. Cardiovascular Health Research Unit, Departments of Medicine, University of Washington.
39. Duke University Department of Medicine, Durham, North Carolina, USA.
40. Department of Human Genetics, University of Michigan, Ann Arbor, Michigan, USA.
41. Vanderbilt University School of Medicine, Center for Human Genetics Research, Nashville, Tennessee, USA.
42. Department of Ophthalmology and Visual Sciences, University of Michigan, Ann Arbor, Michigan, USA. .
43. Brigham and Women's Hospital Department of Medicine and Channing Laboratory, Boston, Massachusetts, USA.

44. Department of Ophthalmology, Harvard Medical School, Massachusetts Eye and Ear Infirmary, Boston, Massachusetts, USA. .
45. Department of Ophthalmology, Duke University School of Medicine, Durham, North Carolina, USA.
46. A list of members is provided in the Supplementary Note.
47. Centre for Vision Research, Department of Ophthalmology and Westmead Millennium Institute, University of Sydney, Westmead, Australia.
48. Center for Human Genetics, Duke University Medical Center, Durham, North Carolina, United States of America.
49. Departments of Ophthalmology and Visual Sciences, University of Iowa, Iowa City, Iowa, USA.
50. Singapore National Eye Centre, Singapore, Singapore.
51. Centre for Vision and Vascular Science, Queen's University Belfast, Belfast, Northern Ireland, United Kingdom.
52. Cornea Genetic Eye Institute, Cedars-Sinai Medical Center, Los Angeles, CA, USA

† Correspondence to:
Assoc Prof. Stuart Macgregor
Queensland Institute of Medical Research
Royal Brisbane Hospital, 300 Herston Road
Brisbane 4029, Australia
Mailing Address:
Queensland Institute of Medical Research
Locked Bag 2000, Herston, QLD 4029, Australia
tel. +61 7 3845 3563
fax. +61 7 3362 0101
stuart.macgregor@qimr.edu.au

Or

Professor Tien Y. Wong
Executive Director, Singapore Eye Research Institute
Singapore National Eye Centre
Professor & Head, Department of Ophthalmology
National University of Singapore & National University Hospital
11 Third Hospital Avenue, Singapore 119228
Tel: +65 6772 5338, Fax: +65 6777 7161
tien_yin_wong@nuhs.edu.sg

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### Supplementary Notes

**Supplementary Table 1. Studies included in the meta-analysis of GWAS on CCT**

| Study | Datasets | N in analysis | CCT (μm) | | Age (years) | | Sex (female%) | Genotyping Platform | Imputation Y/N | Lambdas |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Mean (sd) | Range | Mean (sd) | Range | | | | |
| **Set 1. Samples with European ancestries and unaffected with eye disease (total n=13,057)** | | | | | | | | | | |
| Lu et al (2010) | Australian Twin Study (BATS and TEST) | 1714 (786 families) | 544.3 (35) | 381.5-679.5 | 21.4 (12.6) | 5-90 | 56% | Illumina HumanHap 610W Quad | Y | 1.02 |
| | UK Twin Study | 1759 (1,119 families) | 545.8 (34) | 369-657.5 | 54 (12) | 16-82 | 88.9% | Illumina Hap610w +HumanHap 300K Duo | Y | 1.02 |
| | BMES DNA pools | 143 thin CCT + 146 thick CCT | Thin group: 495.52 (12.2) Thick group: 584.83 (13.6) | | 73.95 (7.5) | 60-95 | 57.3% | Illumina Human 1M-Duo V3 | N | 1.01 |
| | Adelaide blood pools | 106 thin CCT + 105 thick CCT | Thin group: 488.1 (17.9) Thick group: 600.1 (21.9) | | 70.76 (13.3) | 25-93 | 55.5% | Illumina Human 1M-Duo V3 | N | 1.00 |
| Vitart et al (2010) | CROTIA_Vis | 596 | 561.2 (34.6) | 445-670 | 56.2 (14.2) | 18-86 | 59.7% | Illuminia HumanHap 300v1 | Y | 1.01 |
| | CROTIA_Korcula | 849 | 555.6 (36.0) | 457-700 | 56.3 (13.65) | 18-98 | 64.9% | Illumina HumanHap 370CNV-Quad | Y | 1.02 |
| | CROTIA_Split | 349 | 561 (36.3) | 457-662 | 49.9 (14.2) | 18-85 | 55.6% | Illumina 370CNV-Quadv3 | Y | 1.00 |
| | ORCADES | 475 | 536 (33.4) | 430-668 | 54.4 (13.6) | 22-83 | 57.7% | Illumina HumanHap 300v2 + 370CNV-Quad | Y | 1.04 |
| Rotterdam Study | RS-I | 872 | 544.7 (35.27) | 433-695 | 75.93 | 56-100 | 50.1% | Illumina Infinium II HumanHap550chip v3.0 | Y | 1.01 |
| | RS-II | 683 | 549.2 (33.1) | 447-669 | 71.3 | 65-92 | 54.3% | Illumina Infinium II HumanHap550chip v3.0 | Y | 1.01 |
| Western Australia RAINE study | RAINE | 886 | 537.9 (32.26) | 417-647 | 17 | 18-22 | 48.8% | Illumina 660 Quad | Y | 1.01 |
| DeCODE study | DeCODE controls | 299 | 543 (43) | 440-682 | 69 (9) | 50-92 | 58.9% | Illumina HumanHap300 or HumanHapCNV370 | Y | 1.01 |
| Gutenberg Health Study | GHS I | 2796 | 551.4 (34.6) | 442-676 | 55.9 (10.9) | 35 - 74 | 49.0% | Affymetrix Whole genome Human SNP array 6.0 | Y | 1.03 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | GHS II | 1135 | 562.0 (34.0) | 412-675 | 55.0 (10.8) | 35 - 74 | 50.2% | Affymetrix Whole genome Human SNP array 6.0 | Y | 1.02 |
| NEIGHBOR | NEIGHBOR controls | 144 | 557.74 (33.81) | 475.5-656.5 | 62.08 (10.54) | 35-96 | 51.1% | Illumina Human660W_Quad_v1 | N | 1.01 |
| **Set 2. Samples with Asian ancestries and unaffected with eye disease (total n=6,963)** | | | | | | | | | | |
| Vithana et al (2010) | SINDI (Indians) | 2538 | 539.68 (36.19) | 442-1015 | 58.04 (10.01) | 43 - 84 | 48.86 % | Illumina Human610-Quad | Y | 1.04 |
| | SiMES (Malays) | 2542 | 540.66 (33.56) | 421-681 | 59.09 (11.04) | 40 - 80 | 50.55 % | Illumina Human610-Quad | Y | 1.06 |
| Cornes et al (2011) | SCES (Chinese) | 1883 | 552.63 (33.39) | 397-689 | 58.9 (9.63) | 44 - 86 | 49.01 % | Illumina Human610-Quad | Y | 1.02 |
| **Set 3. Glaucoma patients with European ancestries (total n=1,936)** | | | | | | | | | | |
| ANZRAG | ANZRAG POAG patients | 363 | 514 (41.5) | 347-665 | 60 (14.5) | 11-90 | 53% | Illumina Human1M-Omni arrays | Y | 1.01 |
| GLAUGEN | GLAUGEN POAG patients | 305 | 542.65 (35.24) | 450-673.5 | 62.4 (11.2) | 40-87 | 60% | Illumina Human660W_Quad_v1 | N | 1.01 |
| NEIGHBOR | NEIGHBOR POAG patients | 668 | 547.37(36.06) | 450-647 | 61.09 (13.55) | 25-92 | 53% | Illumina Human660W_Quad_v1 | N | 1.00 |
| DeCODE Study | DeCODE glaucoma cases | 409 | 536 (42) | 330 - 647 | 74.9 (9.9) | 37-100 | 52.3% | Illumina HumanHap300 or HumanHapCNV370 | Y | 1.03 |
| UK South Hampton Study | South Hampton POAG cases | 191 | 534.45(34.2) | 416.5-623.5 | 73.94 | 37.4-95.8 | 48.69 % | Affymetrix SNP 6.0 array | N | 1.00 |
| **Set 4. Glaucoma patients with Asian ancestries (n=198)** | | | | | | | | | | |
| HongKong Study | Normal tension glaucoma patients (Chinese) | 198 | 536.9 (34.5) | 445-649 | 64.1 (12.8) | 22-87 | 50.5% | Illumina CNV370Quad | N | 1.00 |

**Supplementary Table 2. Proxies of Table 1 CCT-loci.**

| Leading SNP | Proxy[a] | Distance | $R^2$ | D' | Arrays[b] | Meta-analysis P in Set 1 |
|---|---|---|---|---|---|---|
| rs10189064 | | | | | I3,I5,I6,I6Q,IM,IMD,IC,ICQ,AxM,IWQ | 1.01E-08 |
| | rs10178538 | 288468 | 1 | 1 | I3,I5,I6,I6Q,IM,IMD,IC,ICQ,OQ,IWQ | 1.57E-06 |
| rs3749260 | | | | | I2,I5,I6,I6Q,IM,IMD,AxM,IWQ | 1.26E-08 |
| | rs1870717 | 17808 | 0.941 | 1 | A6 | 1.14E-06 |
| | rs13069468 | 21889 | 0.941 | 1 | I5,I6,I6Q,IM,IMD,CYT,OQ,IWQ,OE | 3.35E-06 |
| rs9822953 | | | | | *Imputed* | 2.70E-08 |
| | rs6441091 | 98491 | 0.848 | 0.921 | I3,I5,I6,I6Q,IM,IMD,IC,ICQ,CM,IWQ | 5.39E-06 |
| | rs6807894 | 99894 | 0.848 | 0.921 | I2,I5,I6,I6Q,IM,IMD,OQ,AxM,IWQ,OE | 3.88E-06 |
| | rs9852504 | 101358 | 0.848 | 0.921 | AS,A6 | 3.90E-04 |
| | rs7617108 | 102116 | 0.848 | 0.921 | AN,A5,A6 | 3.03E-06 |
| | rs13092225 | 116667 | 0.848 | 0.921 | I2,I5,I6,I6Q,IM,IMD,CYT,OQ,IWQ,OE | 3.58E-05 |
| rs1117707 | | | | | *Imputed* | 8.40E-11 |
| | rs10434530 | 13317 | 1 | 1 | OQ,AxM,OE | 8.50E-10 |
| | rs1159105 | 31775 | 0.751 | 0.883 | AS,A5,A6,OQ,AxM,OE | 4.24E-10 |
| rs3118520 | | | | | I6,IM,IMD,CYT,OQ,OE | 3.37E-20 |
| | rs1536482 | 1067 | 0.853 | 1 | I3,I5,I6,I6Q,IM,IMD,IC,ICQ,IWQ | 6.29E-19 |
| | rs3132306 | 1383 | 0.853 | 1 | A6 | 8.89E-20 |
| | rs3118516 | 1803 | 0.853 | 1 | A6,I1 | 1.94E-19 |
| rs7044529 | | | | | I3,I5,I6,I6Q,IM,IMD,IC,ICQ,OQ,IWQ,OE | 1.11E-11 |
| | rs6537942 | 8495 | 1 | 1 | AS,A5,A6,CYT,OQ,OE | 6.85E-11 |
| | rs12554842 | 5356 | 0.748 | 1 | A6 | 4.54E-09 |
| | rs12554098 | 5558 | 0.748 | 1 | I3,I5,I6,I6Q,IM,IMD,IC,ICQ,IBC,CYT,OQ,IWQ,OE | 2.57E-10 |
| rs11145951 | | | | | I3,I5,I6,I6Q,IM,IMD,IC,ICQ,CYT,OQ,IWQ,OE | 9.21E-12 |
| | rs908839 | 3625 | 1 | 1 | A6 | 1.83E-08 |
| | rs7040970 | 1251 | 0.967 | 1 | IM,IMD | 3.91E-11 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | rs11790360 | 5983 | 0.811 | 0.931 | OQ,CM | 3.95E-10 |
| rs1034200 | | | | | I2,I5,I6,I6Q,IM,IMD,OQ,IWQ,OE | 6.13E-10 |
| rs2721051 | | | | | I3,I5,I6,I6Q,IM,IMD,IC,ICQ,OQ,AxM,IWQ,OE | 1.32E-14 |
| | rs2755238 | 614 | 1 | 1 | A6 | 2.86E-14 |
| | rs11616662 | 8582 | 0.915 | 1 | A6 | 1.96E-13 |
| | rs2721043 | 32216 | 0.752 | 0.907 | I2,I5,I6,I6Q,IM,IMD,OQ,AxM,IWQ,OE | 1.01E-11 |
| | rs2755237 | 1455 | 0.736 | 1 | A6,I2,I5,I6,I6Q,IM,IMD,OQ,AxM,IWQ,OE | 1.76E-11 |
| rs785422 | | | | | I3,I5,I6,I6Q,IM,IMD,IC,ICQ,OQ,IWQ,OE | 1.42E-10 |
| | rs785429 | 14347 | 0.786 | 1 | AN,A5,A6,I3,I5,I6,I6Q,IM,IMD,IC,ICQ,OQ,IWQ,OE | 1.71E-09 |
| rs6496932 | | | | | AN,A5,A6,I3,I5,I6,I6Q,IM,IMD,IC,ICQ,CYT,OQ,AxM,IWQ,OE | 6.75E-11 |
| | rs10520600 | 82835 | 0.812 | 1 | AH,I3,I5,I6,I6Q,IM,IMD,IC,ICQ,IWQ | 2.68E-09 |
| | rs12901648 | 126151 | 0.81 | 0.947 | A6,I2,I5,I6,I6Q,IM,IMD,OQ,AxM,IWQ,OE | 1.42E-06 |
| | rs10163187 | 44951 | 0.729 | 1 | A6 | 5.45E-10 |
| rs2034809 | | | | | I3,I5,I6,I6Q,IM,IMD,IC,ICQ,OQ,IWQ,OE | 7.50E-05 |
| rs930847 | | | | | AS,A5,A6,I2,I5,I6,I6Q,IM,IMD,OQ,IWQ,OE | 3.73E-13 |
| rs752092 | | | | | A6,I2,I5,I6,I6Q,IM,IMD,CYT,OQ,IWQ,OE | 5.87E-09 |
| | rs8043243 | 10481 | 0.897 | 1 | AG,I3,I5,I6,I6Q,IM,IMD,IC,ICQ,IWQ | 9.33E-06 |
| rs6540223 | | | | | AN,A5,A6,OQ | 1.27E-39 |
| | rs7500824 | 21945 | 1 | 1 | AS,A5,A6,OQ,OE | 7.08E-39 |
| | rs12447690 | 23312 | 0.967 | 1 | I3,I5,I6,I6Q,IM,IMD,IC,ICQ,IWQ,OE | 8.42E-37 |
| | rs12448211 | 9077 | 0.78 | 0.929 | AN,A5,A6,IM,IMD,CYT | 2.59E-38 |
| | rs9938149 | 10204 | 0.777 | 0.897 | AS,A5,A6,I2,I5,I6,I6Q,IM,IMD,IWQ,OE | 6.75E-37 |
| rs2323457 | | | | | A6,I3,I5,I6,I6Q,IM,IMD,IC,ICQ,IWQ | 4.68E-08 |
| | rs12940030 | 6826 | 1 | 1 | I2,I5,I6,I6Q,IM,IMD,CYT,OQ,IWQ,OE | 5.70E-08 |
| | rs4792534 | 10659 | 1 | 1 | AS,A5,A6 | 9.60E-08 |
| | rs4792535 | 10940 | 1 | 1 | I2,I5,I6,I6Q,IM,IMD,IWQ | 7.22E-08 |

a. The proxies are queried using SNAP (http://www.broadinstitute.org/mpg/snap/ldsearch.php). The proxies are restricted to be less than 500kb away and in high linkage disequilibrium ($R^2$>0.7 in HapMap 2 CEU set) with the leading SNP.

b. Refer to SNAP (http://www.broadinstitute.org/mpg/snap/ldsearch.php) for array abbreviations.

**Supplementary Table 3. Association of Table 1 CCT-loci in Set 2 Asian samples.**

| Locus[a] | Chr | LeadingSNP Or proxies[b,c] | $R^{2,d}$ | A1,A2 | Meta analysis of SINDI (n=2,538 Indians), SIMES (n=2,542 Malays), SCES (n=1,883 Chinese) | | | | | | Same direction as in Set 1? |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | AF1[e] | Beta (se) | P | $I^2$ | P_Het | Effect directions[e] | |
| ***USP37*** | 2 | rs10189064 | | A,G | Na | Na | Na | Na | Na | Na | Na |
| ***GPR15*** | 3 | rs3749260 | | A,C | 0.16,0.13,0.10 | -0.00 (0.02) | 0.88 | 62.4 | 0.07 | +-+ | Y |
| ***TIPARP*** | 3 | rs9822953 | | T,C | | | | | | | |
| | | rs1430408 | 0.87 | A,G | 0.44,0.79,0.81 | 0.04 (0.02) | 0.03 | 32.5 | 0.23 | ++- | Y |
| ***CWC27- ADAMTS6*** | 5 | rs1117707 | | A,G | | | | | | | |
| | | rs264739 | 0.66 | T,C | 0.52,0.67,0.59 | -0.03 (0.02) | 0.11 | 0 | 0.93 | --- | Y |
| *RXRA-COL5A1* | 9 | rs3118520 | | A,G | | | | | | | |
| | | rs1536482 | 0.94 | A,G | 0.45,0.25,0.22 | -0.08 (0.02) | 8.9e-6 | 0 | 0.61 | --- | Y |
| *COL5A1* | 9 | rs7044529 | | T,C | 0.26,0.16,0.12 | -0.05 (0.02) | 0.01 | 61.2 | 0.08 | --+ | Y |
| ***LCN12-PTGDS*** | 9 | rs11145951 | | T,C | 0.58,0.80,0.85 | 0.04 (0.02) | 0.02 | 28 | 0.25 | +++ | Y |
| *FGF9-SGCG* | 13 | rs1034200 | | A,C | 0.19,0.31,0.31 | 0.02 (0.02) | 0.26 | 0 | 0.61 | -++ | Y |
| *Near FOXO1 (3')* | 13 | rs2721051 | | T,C | 0.03,Na, Na | -0.13(0.07) | 0.08 | Na | Na | -?? | Y |
| ***Near TJP1 (5')*** | 15 | rs785422 | | T,C | 0.10,0.05, Na | -0.10 (0.04) | 7.6e-3 | 0 | 0.54 | --? | Y |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *Near AKAP13 (5')* | 15 | rs6496932 | | A,C | 0.40,0.35,0.31 | -0.06 (0.02) | 3.0e-4 | 0 | 0.55 | --- | Y |
| *LRRK1* | 15 | rs2034809 | | A,G | 0.45,0.76,0.78 | -0.06 (0.02) | 4.2e-4 | 0 | 0.44 | --- | Y |
| *LRRK1* | 15 | rs930847 | | T,G | 0.83,0.61,0.80 | -0.11 (0.02) | 3.4e-8 | 0 | 0.85 | --- | Y |
| *CHSY1* | 15 | rs752092 | | A,G | 0.74,0.80,0.83 | -0.05 (0.02) | 0.02 | 15.1 | 0.31 | --+ | Y |
| *BANP-ZNF469* | 16 | rs6540223 | | T,C | | | | | | | |
| | | rs9938149 | 0.54 | A,C | 0.66,0.83,0.92 | 0.16 (0.02) | 3.1e-15 | 44.5 | 0.17 | +++ | Y |
| ***HS3ST3B1-PMP22*** | 17 | rs2323457 | | A,C | 0.34,0.50,0.44 | -0.06 (0.02) | 8.5e-4 | 0 | 0.45 | --- | Y |

a. Locus assigned to the RefSeq protein-coding gene within or near (noted near) the association signal interval (defined by linkage disequilibrium plot using a measure r2 > 0.9 with the leading SNP implemented in SNAP using the CEU reference). The locus was assigned to the interval defined by the two flanking RefSeq protein-coding genes if clearly intergenic. Novel loci for both European and Asian populations are marked in bold.

b. Some of the leading SNPs are rare in these Asian populations, for example rs10189064 is rare in all three populations, rs2721051 is rare in SIMES and SCES, and rs785422 is rare in SCES. The results are listed as missing ("Na").

c. The search of proxies is restricted to the Illumina Human610-Quad array, as it was the array used to genotype these samples.

d. $R^2$ between the leading SNP and its proxy is based on HapMap JPT+CHB reference.

e. The allele frequency column ("AF1") and effect direction column ("Effect directions") are listed in the order of SINDI, SIMES, SCES.

**Supplementary Table 4. Association of Table 2 CCT-loci in clinical sample sets: Set 3 (European) and Set 4 (Asian).**

| | | | | | Set 3 – POAG cases (European) (N=1,936) | | | | | Set 4 - NTG cases (Asian) (N=194)[d] | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Locus[a]** | **Chr** | **Leading SNP** | **A1/A2** | **basepair** | **AF1** | **Beta** | **Se** | **P** | **Same dir?[c]** | **AF1** | **Beta** | **Se** | **P** | **Same dir?[c]** |
| *COL8A2* | 1 | rs96067 | A/G | 36344507 | 0.811 | 0.027 | 0.043 | 0.529 | Y | 0.472 | 0.244 | 0.097 | 0.012 | Y |
| ***COL4A3*** | 2 | rs7606754 | A/G | 227843424 | 0.333 | -0.008 | 0.038 | 0.830 | Y | Na | Na | Na | Na | Na |
| ***FNDC3B*** | 3 | rs4894535 | T/C | 173478299 | 0.163 | -0.019 | 0.047 | 0.687 | Y | 0.335 | -0.127 | 0.108 | 0.241 | Y |
| ***TBL1XR1-KCNMB2[b]*** | 3 | rs7620503 | T/C | 178786992 | 0.395 | -0.037 | 0.039 | 0.341 | Y | Na | Na | Na | Na | Na |
| ***NR3C2*** | 4 | rs3931397 | T/G | 149298947 | 0.071 | -0.075 | 0.078 | 0.338 | Y | 0.078 | 0.061 | 0.196 | 0.756 | N |
| *ADAMTS6* | 5 | rs2307121 | T/C | 64661268 | 0.340 | 0.103 | 0.034 | 0.002 | Y | 0.177 | 0.081 | 0.128 | 0.527 | Y |
| *FAM46A-IBTK* | 6 | rs1538138 | T/C | 82851313 | 0.262 | -0.109 | 0.039 | 0.005 | Y | 0.283 | -0.136 | 0.111 | 0.222 | Y |
| ***VKORC1L1*** | 7 | rs11763147 | A/G | 64964256 | 0.444 | 0.048 | 0.036 | 0.182 | Y | 0.220 | 0.074 | 0.123 | 0.545 | Y |
| *C7orf42* | 7 | rs4718428 | T/G | 66058881 | 0.644 | 0.080 | 0.040 | 0.044 | Y | 0.331 | 0.098 | 0.104 | 0.349 | Y |
| *MPDZ-NF1B* | 9 | rs1324183 | A/C | 13547491 | 0.198 | -0.126 | 0.048 | 0.009 | Y | Na | Na | Na | Na | Na |
| ***LPAR1*** | 9 | rs1007000 | T/C | 112702502 | 0.213 | 0.054 | 0.042 | 0.197 | Y | 0.187 | 0.123 | 0.129 | 0.339 | Y |
| *RXRA-COL5A1* | 9 | rs1536482 | A/G | 136580349 | 0.347 | -0.097 | 0.041 | 0.018 | Y | 0.220 | 0.052 | 0.121 | 0.670 | N |
| *COL5A1* | 9 | rs7044529 | T/C | 136707872 | 0.152 | -0.172 | 0.048 | 3.1E-04 | Y | 0.131 | -0.017 | 0.151 | 0.910 | Y |
| *LCN12-PTGDS* | 9 | rs11145951 | T/C | 138980085 | 0.496 | 0.080 | 0.038 | 0.035 | Y | 0.874 | 0.132 | 0.152 | 0.385 | Y |
| ***ARID5B*** | 10 | rs7090871 | T/C | 63500292 | 0.613 | 0.064 | 0.039 | 0.103 | Y | 0.611 | 0.114 | 0.102 | 0.266 | Y |
| ***ARHGAP20-POU2AF1*** | 11 | rs4938174 | A/G | 110418450 | 0.283 | 0.140 | 0.038 | 2.2E-04 | Y | 0.101 | 0.152 | 0.163 | 0.352 | Y |
| ***Near GLT8D2 (5')*** | 12 | rs1564892 | A/G | 102969872 | 0.785 | -0.100 | 0.085 | 0.238 | Y | Na | Na | Na | Na | Na |
| *FGF9-SGCG* | 13 | rs1034200 | A/C | 22126691 | 0.266 | 0.096 | 0.039 | 0.014 | Y | Na | Na | Na | Na | Na |
| *Near FOXO1(3')* | 13 | rs2721051 | T/C | 40008884 | 0.108 | -0.105 | 0.054 | 0.051 | Y | Na | Na | Na | Na | Na |
| *Near TJP1(5')* | 15 | rs785422 | T/C | 27961177 | 0.097 | -0.038 | 0.058 | 0.518 | Y | Na | Na | Na | Na | Na |
| ***SMAD3*** | 15 | rs12913547 | T/C | 65254561 | 0.784 | -0.054 | 0.039 | 0.175 | Y | Na | Na | Na | Na | Na |
| *Near AKAP13 (5')* | 15 | rs6496932 | A/C | 83626571 | 0.183 | 0.016 | 0.042 | 0.705 | N | 0.303 | -0.099 | 0.111 | 0.373 | N |
| *LRRK1* | 15 | rs930847 | T/G | 99376085 | 0.771 | -0.061 | 0.039 | 0.118 | Y | Na | Na | Na | Na | Na |
| *CHSY1* | 15 | rs752092 | A/G | 99599457 | 0.675 | -0.065 | 0.035 | 0.062 | Y | Na | Na | Na | Na | Na |
| *BANP-ZNF469* | 16 | rs9938149 | A/C | 86889141 | 0.613 | 0.129 | 0.037 | 4.6E-04 | Y | Na | Na | Na | Na | Na |

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *HS3ST3B1-PMP22* | 17 | rs12940030 | T/C | 14501741 | 0.713 | 0.049 | 0.037 | 0.189 | Y | Na | Na | Na | Na | Na |

a. Locus assigned to the RefSeq protein-coding gene within or near (noted near) the association signal interval (defined by linkage disequilibrium plot using a measure r2 > 0.9 with the leading SNP implemented in SNAP using the CEU reference). The locus was assigned to the interval defined by the two flanking RefSeq protein-coding genes if clearly intergenic. Additional novel loci for both European and Asian populations are marked in bold. The locus COL4A3 was suggested in a set of Croatian samples but that had not reached statistical significance.
b. The leading SNP is within a validated non coding mRNA: *LINC00578.*
c. Effect directions are compared with the ones reported in Table 2. “Y” indicates the effect direction is the same; “N” indicates the SNP has an opposite effect direction.
d. Na’s in Set 4 results indicate that either the SNP is not genotyped or it is rare in these glaucoma patients with Han Chinese ancestry.

**Supplementary Table 5. VEGAS gene-based results on meta of European samples.**

| Chr | Gene[a] | Num. SNPs | Num. Permutation | Start | Stop | Permutated P | Rank | Leading SNP | P for leading SNP |
|---|---|---|---|---|---|---|---|---|---|
| 5 | *CWC27* | 313 | 1E+06 | 64100510 | 64350346 | <1e-6 | 1 | rs3797046 | 3.2E-10 |
| 5 | *ADAMTS6* | 357 | 1E+06 | 64480318 | 64813460 | <1e-6 | 1 | rs386188 | 1.2E-10 |
| 9 | *COL5A1* | 331 | 1E+06 | 136673472 | 136876509 | 3.0E-06 | 3 | rs7044529 | 5.4E-12 |
| 9 | *RXRA* | 157 | 1E+03 | 136358230 | 136472252 | 0.53 | 10283 | rs11185717 | 3.8E-03 |
| 9 | *PTGDS* | 46 | 1E+06 | 138991776 | 138996015 | 7.0E-06 | 6 | rs11145951 | 1.3E-11 |
| 9 | *LCN12* | 52 | 1E+06 | 138966588 | 138969770 | 6.1E-05 | 16 | rs11145951 | 1.3E-11 |
| 7 | *GUSB* | 40 | 1E+06 | 65063107 | 65084681 | 8.0E-06 | 7 | rs1701760 | 1.6E-07 |
| 7 | *VKORC1L1* | 43 | 1E+06 | 64975691 | 65057235 | 8.0E-06 | 8 | rs11763147 | 1.8E-07 |
| 15 | *CHSY1* | 165 | 1E+06 | 99533454 | 99609649 | 4.0E-05 | 12 | rs752092 | 1.6E-08 |
| 15 | *LRRK1* | 266 | 1E+05 | 99276982 | 99427840 | 4.5E-03 | 174 | rs930847 | 9.3E-13 |
| 15 | *AKAP13* | 610 | 1E+06 | 83724874 | 84093590 | 5.8E-05 | 15 | rs4843049 | 4.5E-10 |
| 7 | *RABGEF1* | 84 | 1E+06 | 65843077 | 65913883 | 1.1E-04 | 18 | rs2016325 | 8.7E-07 |
| 7 | *C7orf42* | 66 | 1E+06 | 66023637 | 66060973 | 4.3E-04 | 48 | rs4718424 | 1.5E-05 |
| 7 | *KCTD7* | 66 | 1E+06 | 65731379 | 65743252 | 6.4E-04 | 57 | rs3764903 | 3.9E-06 |
| 3 | *FNDC3B* | 386 | 1E+06 | 173241079 | 173601181 | 1.3E-04 | 19 | rs6445055 | 9.5E-08 |
| 15 | *SMAD3* | 253 | 1E+06 | 65145248 | 65274587 | 2.5E-04 | 30 | rs7181556 | 4.8E-07 |
| 9 | *LPAR1* | 345 | 1E+06 | 112675874 | 112840186 | 2.7E-04 | 33 | rs1409684 | 1.7E-06 |
| 2 | *COL4A3* | 308 | 1E+06 | 227737524 | 227887751 | 3.3E-04 | 39 | rs7606754 | 2.8E-07 |
| 12 | *GLT8D2* | 184 | 1E+06 | 102906894 | 102968045 | 5.6E-04 | 53 | rs1564892 | 1.4E-07 |
| 12 | *HCFC2* | 104 | 1E+05 | 102982365 | 103024433 | 0.01 | 365 | rs1564892 | 1.4E-07 |
| 13 | *FOXO1* | 157 | 1E+05 | 40027800 | 40138734 | 3.3E-03 | 147 | rs2721051 | 1.5E-14 |
| 3 | *GPR15* | 110 | 1E+05 | 99733567 | 99734650 | 4.9E-03 | 179 | rs3749260 | 1.2E-08 |
| 10 | *ARID5B* | 212 | 1E+05 | 63331448 | 63526709 | 6.3E-03 | 221 | rs4948502 | 7.1E-07 |
| 11 | *ARHGAP20* | 260 | 1E+05 | 109952975 | 110088661 | 6.4E-03 | 222 | rs11213578 | 1.8E-04 |
| 11 | *C11orf53* | 140 | 1E+03 | 110631916 | 110662182 | 0.58 | 11125 | rs12280810 | 2.8E-02 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 1 | *COL8A2* | 40 | 1E+05 | 36333432 | 36338437 | 0.05 | 1241 | rs7550047 | 2.3E-03 |
| 1 | *ADPRHL2* | 35 | 1E+05 | 36327072 | 36332120 | 0.06 | 1405 | rs7550047 | 2.3E-03 |
| 1 | *TRAPPC3* | 49 | 1E+05 | 36374759 | 36387654 | 0.09 | 1912 | rs7550047 | 2.3E-03 |
| 4 | *NR3C2* | 384 | 1E+03 | 149219364 | 149583093 | 0.16 | 3314 | rs3931397 | 3.6E-06 |
| 16 | *ZNF469* | 70 | 1E+03 | 87021379 | 87034666 | 0.18 | 3599 | rs8051284 | 2.3E-03 |
| 16 | *BANP* | 111 | 1E+03 | 86542538 | 86668425 | 0.39 | 7611 | rs9924813 | 3.0E-03 |
| 13 | *FGF9* | 110 | 1E+03 | 21143874 | 21174186 | 0.27 | 5383 | rs7317531 | 3.5E-02 |
| 3 | *TBL1XR1* | 149 | 1E+03 | 178221235 | 178397742 | 0.38 | 7407 | rs9841983 | 3.5E-02 |
| 3 | *KCNMB2* | 457 | 1E+03 | 179736917 | 180044911 | 0.73 | 13783 | rs6789294 | 0.01 |
| 15 | *TJP1* | 134 | 1E+03 | 27779648 | 27901998 | 0.43 | 8284 | rs939980 | 7.1E-04 |
| 6 | *IBTK* | 134 | 1E+03 | 82936674 | 83014167 | 0.47 | 8995 | rs10943857 | 9.0E-05 |
| 6 | *FAM46A* | 153 | 1E+03 | 82512165 | 82519147 | 0.48 | 9167 | rs194914 | 4.9E-02 |
| 2 | *USP37* | 101 | 1E+03 | 219023217 | 219141328 | 0.63 | 11948 | rs10189064 | 1.6E-08 |
| 17 | *HS3ST3B1* | 156 | 1E+03 | 14145230 | 14190217 | 0.64 | 12193 | rs3848445 | 5.8E-03 |

This gene-based test was run on Set 1 meta-analysis results, therefore HapMap 2 CEU was used as the reference.

a. The genes were selected as known loci for CCT, novel loci and their neighbouring genes (were placed together in each block of the table) identified in this study.

**Supplementary Table 6. VEGAS-Pathway analysis results on meta of European samples**.

| GO_ID | GO_term | P[a] | Genes |
|---|---|---|---|
| GO:0005581 | collagen | 1.0E-05 (0.046) | COL16A1,COL9A2,COL24A1,COL11A1,COL5A2,COL4A3,COL6A3,COL7A1,COL8A1,LOX,TNXB,COL11A2,COL9A1,COL12A1,COL10A1,COL1A2,COL14A1,COL15A1,COL27A1,COL5A1,COL13A1,COL2A1,LUM,COL4A2,COL1A1,COL5A3,COL9A3,COL6A1 |
| GO:0031012 | extracellular matrix | 3.2E-05 (0.15) | VWA1,MFAP2,WNT4,MATN1,COL16A1,COL8A2,COL9A2,LEPRE1,PODN,COL24A1,F3,COL11A1,NTNG1,WNT2B,ADAMTSL4,RPTN,BCAN,ADAMTS4,DPT,TNR,LAMC2,HMCN1,LAD1,OPTC,LAMB3,USH2A,TGFB2,WNT3A,NID1,ZP4,PXDN,MATN3,EMILIN1,LTBP1,VIT,EFEMP1,FBLN7,COL5A2,FN1,WNT10A,COL4A3,COL6A3,GPC1,CHL1,TIMP4,WNT7A,COLQ,EFHB,CRTAP,COL7A1,DAG1,WNT5A,ADAMTS9,COL8A1,IMPG2,CCDC80,COL6A6,MUC4,SPON2,CPZ,SOD3,ENAM,ADAMTS3,MEPE,SNCA,NPNT,PRSS12,C4orf31,SPOCK3,ADAMTS16,ADAMTS12,SLC1A3,EGFLAM,FGF10,ERBB2IP,THBS4,HAPLN1,LOX,FBN2,ADAMTS19,TGFBI,SPOCK1,WNT8A,RELL2,FGF1,SPARC,GABRA6,ADAMTS2,GPLD1,C6orf15,TNXB,COL11A2,VEGFA,CRISP3,TINAG,DST,COL9A1,COL12A1,IMPG1,LAMA4,COL10A1,LAMA2,CTGF,SERAC1,SMOC2,COL28A1,VWC2,ELN,ZP3,TFPI2,COL1A2,GPC2,EMID2,RELN,LAMB4,WNT2,WNT16,PTPRZ1,PRSS2,LPL,MMP16,MATN2,CTHRC1,NOV,COL14A1,OC90,FREM1,ADAMTSL1,MAMDC2,ECM2,COL15A1,COL27A1,TNC,OLFML2A,LAMC3,NTNG2,ADAMTSL2,COL5A1,ENTPD2,UCMA,RBP3,COL13A1,ADAMTS14,SPOCK2,SFTPD,MMRN2,CRTAC1,WNT8B,KAZALD1,COL17A1,SMC3,TECTB,FGFR2,MMP21,MUC5AC,MMP26,SPON1,NAV2,CD44,HSD17B12,ZP1,FLRT1,CD248,WNT11,MMP13,TECTA,ADAMTS15,WNT5B,VWF,MFAP5,GRIN2B,MGP,ADAMTS20,COL2A1,WNT1,MMP19,DCN,NTN4,MMP17,FGF9,POSTN,FREM2,GPC6,COL4A2,ANG,MMP14,COCH,NID2,BMP4,LGALS3,SMOC1,PAPLN,LTBP2,TGFB3,FLRT2,FBLN5,SERPINA1,THBS1,MFAP1,FBN1,ANXA2,CILP,THSD4,LOXL1,ADAMTS7,ADAMTSL3,HAPLN3,ADAMTS17,PCSK6,NTN3,MMP25,OTOA,SPN,PRSS36,MMP2,MMP15,GFOD2,ADAMTS18,CRISPLD2,NTN1,MFAP4,VTN,MMP28,WNT9B,CHAD,LGALS3BP,EMILIN2,LAMA1,LAMA3,ADAMTSL5,ADAMTS10,COL5A3,CALR,PODNL1,CILP2,APLP1,SPINT2,LTBP4,TGFB1,FLRT3,MMP24,EMILIN3,PI3,MMP9,BMP7,LAMA5,COL9A3,ADAMTS5,SOD1,TFF3,COL6A2,DGCR6,MMP11,TFIP11,EMID1,TIMP3,LGALS1,WNT7B |
| GO:0005578 | proteinaceous extracellular matrix | 4.6E-05 (0.21) | VWA1,MFAP2,WNT4,MATN1,COL16A1,COL8A2,COL9A2,LEPRE1,PODN,COL24A1,COL11A1,NTNG1,WNT2B,ECM1,RPTN,BCAN,ADAMTS4,DPT,TNR,LAMC2,HMCN1,LAD1,OPTC,LAMB3,USH2A,WNT3A,NID1,ZP4,MATN3,EMILIN1,LTBP1,VIT,EFEMP1,FBLN7,COL5A2,FN1,WNT10A,COL4A3,COL6A3,GPC1,CHL1,TIMP4,WNT7A,COLQ,EFHB,CRTAP,COL7A1,DAG1,WNT5A,ADAMTS9,COL8A1,IMPG2,CCDC80,COL6A6,MUC4,SPON2,CPZ,ENAM,ADAMTS3,MEPE,SNCA,NPNT,SPOCK3,ADAMTS16,ADAMTS12,SLC1A3,EGFLAM,ERBB2IP,THBS4,HAPLN1,LOX,FBN2,ADAMTS19,TGFBI,SPOCK1,WNT8A,RELL2,FGF1,SPARC,ADAMTS2,GPLD1,C6orf15,TNXB,COL11A2,VEGFA,CRISP3,TINAG,DST,COL9A1,COL12A1,IMPG1,LAMA4,COL10A1,LAMA2,CTGF,SMOC2,COL28A1,VWC2,ELN,ZP3,TFPI2,COL1A2,GPC2,EMID2,RELN,LAMB4,WNT2,WNT16,PTPRZ1,MMP16,MATN2,CTHRC1,TNFRSF11B,COL14A1,OC90,FREM1,ADAMTSL1,MAMDC2, |

| | | | |
|---|---|---|---|
| | | | ECM2,COL15A1,COL27A1,TNC,LAMC3,NTNG2,ADAMTSL2,COL5A1,ENTPD2,UCMA,RBP3,COL13A1,ADAMTS14,SPOCK2,SFTPD,MMRN2,CRTAC1,WNT8B,KAZALD1,COL17A1,SMC3,TECTB,MMP21,MUC5AC,MMP26,SPON1,NAV2,ZP1,FLRT1,CD248,WNT11,MMP13,TECTA,ADAMTS15,WNT5B,VWF,MFAP5,MGP,ADAMTS20,COL2A1,WNT1,MMP19,DCN,NTN4,MMP17,FGF9,POSTN,FREM2,GPC6,COL4A2,ANG,MMP14,COCH,NID2,BMP4,LGALS3,SMOC1,PAPLN,LTBP2,FLRT2,FBLN5,SERPINA1,MFAP1,FBN1,ANXA2,CILP,THSD4,LOXL1,ADAMTS7,ADAMTSL3,HAPLN3,ADAMTS17,NTN3,MMP25,OTOA,SPN,PRSS36,MMP2,MMP15,GFOD2,ADAMTS18,NTN1,MFAP4,VTN,MMP28,WNT9B,CHAD,LGALS3BP,EMILIN2,LAMA1,LAMA3,ADAMTSL5,ADAMTS10,COL5A3,CALR,PODNL1,CILP2,APLP1,LTBP4,TGFB1,FLRT3,MMP24,EMILIN3,PI3,MMP9,LAMA5,COL9A3,ADAMTS5,TFF3,COL6A2,DGCR6,MMP11,TFIP11,EMID1,TIMP3,LGALS1,WNT7B |
| GO:0044420 | extracellular matrix part | 5.0E-05 (0.23) | VWA1,MFAP2,HSPG2,COL16A1,COL8A2,COL9A2,COL24A1,COL11A1,LAMC2,HMCN1,LAD1,LAMB3,USH2A,NID1,COL5A2,COL4A3,COL6A3,COLQ,COL7A1,DAG1,COL8A1,CCDC80,AMTN,SNCA,PRSS12,SLC1A3,EGFLAM,ERBB2IP,LOX,RELL2,SPARC,GABRA6,TNXB,COL11A2,VEGFA,TINAG,DST,COL9A1,COL12A1,LAMA4,COL10A1,LAMA2,SMOC2,COL28A1,VWC2,COL1A2,ACHE,LAMB4,COL14A1,FREM1,COL15A1,COL27A1,TNC,LAMC3,COL5A1,ENTPD2,COL13A1,MMRN2,COL17A1,SMC3,MUC5AC,EFEMP2,MFAP5,GRIN2B,COL2A1,LUM,NTN4,FGF9,FREM2,COL4A2,ANG,NID2,SMOC1,PAPLN,MFAP1,FBN1,ANXA2,CILP,SPN,NTN1,MFAP4,COL1A1,TIMP2,LAMA1,LAMA3,COL5A3,APLP1,LAMA5,COL9A3,ADAMTS1,TFF3,COL6A1,TIMP3 |
| GO:0005583 | fibrillar collagen | 5.2E-05 (0.24) | COL11A1,COL5A2,TNXB,COL11A2,COL1A2,COL5A1,COL2A1,LUM,COL1A1,COL5A3 |
| GO:0030199 | collagen fibril organization | 0.0002 (0.92) | COL11A1,DPT,TGFB2,COL5A2,ADAMTS3,LOX,ADAMTS2,FOXC1,COL11A2,COL12A1,COL1A2,COL14A1,TGFBR1,LMX1B,COL5A1,SERPINH1,COL2A1,LUM,ANXA2,FOXC2,NF1,COL1A1,COL5A3 |
| GO:0044236 | multicellular organismal metabolic process | 0.0002 (0.92) | COL3A1,TIPARP,ADAMTS3,GHR,ADAMTS2,TNXB,TRAM2,PRSS2,MMP16,CEL,COL5A1,ADAMTS14,MMP26,SERPINH1,MMP13,APOA4,MMP19,PLA2G1B,P2RX7,MNAT1,HIF1A,MMP2,ACACA,COL1A1,ACE,PRTN3,PEPD,KLK6,MMP9,MMP11 |
| GO:0017022 | myosin binding | 0.0004 (1) | ACTA1,CXCR4,MLPH,MYRIP,MYL3,RHOA,GPR98,STX1A,CALD1,ARFGEF1,TRIM32,MYBPC3,MYL2,ACTC1,TRPM7,RAB27A,MYL4,GIPC1,SNAP25,MYLK2,ARFGEF2,TRIOBP |

This pathway analysis was based on the results from gene-based test which was run on Set 1 meta-analysis results.
a. Empirical P-value from 500,000 simulations. P-values after Bonferroni correction for multiple testing were included in the brackets.

**Supplementary Table 7. Magenta pathway analysis results on meta of European samples.**

| GO pathway | Nominal P[a] | FDR[a] | FLAGGED_GENE_NAMES |
|---|---|---|---|
| myosin binding | 3.4E-05 | 0.02 | ACTA1,ACTC1,RHOA,CALD1,MYBPC3,SNAP25,STX1A,ARFGEF2,ARFGEF1,GIPC1,TRIM32,MYRIP,TRPM7,GPR98 |
| proteinaceous extracellular matrix | 5.2E-05 | 0.4 | ACAN,AMBN,AMELX,AMELY,BGN,BMP4,CALR,CHAD,CHI3L1,COL6A1,COL6A2,COL6A3,COL8A2,COL9A1,COL9A2,COL9A3,COL12A1,COL16A1,COL19A1,COMP,HAPLN1,VCAN,CTGF,DAG1,DCN,COCH,DMP1,DPT,EPYC,DSPP,ECM2,ECM1,ELN,FBLN1,FBLN2,FBN1,FBN2,EFEMP1,GPC4,FGF1,GPC5,FMOD,FN1,GPC3,GPC1,GPLD1,IMPG1,KAL1,LGALS1,LGALS3,LGALS3BP,LOXL1,LTBP1,LTBP2,LUM,MATN1,MATN2,MATN3,MFAP1,MFAP2,MFAP4,MGP,MMP1,MMP2,MMP3,MMP7,MMP8,MMP9,MMP10,MMP11,MMP12,MMP13,MMP16,MMP17,MMP19,MUC4,NTN3,OMD,OGN,TNFRSF11B,VIT,SERPINA1,PI3,PRELP,RELN,PTPRZ1,SFTPD,SPARC,SPOCK1,TECTB,TECTA,TFF3,TGFB1,TGFBI,TIMP1,TIMP4,TNR,TNXB,COL14A1,VEGFA,VTN,VWF,WNT1,WNT2,WNT3,WNT5A,WNT6,WNT7A,WNT7B,WNT8A,WNT8B,WNT10B,WNT11,WNT2B,WNT9A,WNT9B,ZP2,ZP3,PXDN,TFPI2,MFAP5,DGCR6,SPARCL1,LTBP4,CILP,MMP23B,CPZ,MMP20,ADAMTS4,ADAMTS3,ADAMTS2,ADAMTSL2,SPOCK2,GPC6,ENAM,LAMC3,CRISP3,SPON2,SPON1,CRTAP,FBLN5,POSTN,CHL1,MMP24,KERA,ADAMTS13,ADAMTS8,ADAMTS5,EMILIN1,ADAMTS7,ADAMTS6,NTNG1,ZP1,FLRT3,FLRT2,FLRT1,TFIP11,OPTC,SPOCK3,IMPG2,ANGPTL4,WNT16,WNT4,ASPN,CRTAC1,MMP26,MEPE,ADAMTS9,CD248,ADAMTSL3,ZP4,HAPLN2,NYX,BCAN,TNN,MMP27,LEPRE1,MMP25,MMP28,THSD4,PODNL1,ADAMTS20,WNT10A,WNT5B,GFOD2,COL21A1,ADAMTS12,ADAMTS10,EMILIN2,FBN3,NTNG2,WNT3A,EMILIN3,ADAMTSL1,CTHRC1,RPTN,PODN,EMID1,FBLN7,COL6A6,EMID2,ADAMTS14,HAPLN3,OTOA,PRSS36,CILP2,CHADL,ADAMTS15,ADAMTS16,ADAMTS17,ADAMTS18,ADAMTS19,UCMA,GPC2,NPNT,COL6A5,LAMA1,ADAMTSL5,AMTN,HAPLN4,SFTPA1,SFTPA2,OC90 |
| integrin binding | 1.0E-04 | 0.4 | ACTN4,ACTN1,ACTN2,ACTN3,ADAM10,DST,CALR,COL3A1,COL3A1,COL4A3,COL4A3,COL5A1,COL16A1,CTGF,DMP1,ECM2,FCER2,ADAM2,ICAM1,ICAM2,ICAM3,ICAM4,ILK,ITGA6,ITGA1,ITGA2,ITGA5,ITGB3,ITGB6,L1CAM,LAMA5,LYN,ADAM11,MFGE8,SYK,ADAM17,TGFBI,THBS1,THBS4,THY1,TIMP2,TNXB,VCAM1,VWF,LTBP4,ADAM23,ADAM9,ADAM9,ADAM9,EDIL3,GPNMB,FBLN5,CD226,ADAMTS13,ADAMTS8,ADAMTS5,NISCH,EGFL6,ADAMDEC1,ANGPTL3,ADAM22,ERBB2IP,TNN,FERMT3 |
| integral to endoplasmic reticulum membrane | 3.1E-03 | 1 | AMFR,ASPH,BNIP1,CLN3,ERN1,EXT1,G6PC,HSPA5,RRBP1,RTN1,RTN2,SSR3,STIM1,UPK2,WFS1,DPM2,SGPL1,EDEM1,PIGK,DHRS9,DOLK,SACM1L,SLC35D1,LRIT1,BSCL2,SPCS1,SEC61A1,DERL2,PIGT,DPM3,ACER3,SELS,RTN4,ASPHD2,DOLPP1,PORCN,ELOVL6,DERL1,DERL3,PIGU,ASPHD1,MBOAT4 |
| blood vessel development | 4.8E-03 | 1 | AGT,AKT1,ATP7A,CDX2,CDX4,CHM,COL1A1,COL1A2,COL3A1,COL5A1,CRKL,DHCR7,DLX3,FOXC1,FOXC2,FOXS1,FOXO1,GJA4,GJA5,ITGAV,LAMA4,LMO2,LOX,PKD1,PROP1,PSEN1,PTK2,TBX3,TCF7L2,TGFBR2,PPAP2B,CITED2,JMJD6,EGFL7,CHD7,MIB1,ESX1 |

| | | | |
|---|---|---|---|
| metallopeptidase activity | 5.2E-03 | 1 | ACY1,ADAM8,ADAM10,ADAM10,ANPEP,BMP1,CPA1,CPA2,CPA3,CPB1,CPB2,CPD,CPE,CPM,CPN1,ACE,ACE,FOLH1,ADAM2,LNPEP,LTA4H,ADAM11,MME,PAPPA,PAPPA,CHMP1A,ADAM17,TAF2,ZNF708,ADAM12,MMP23B,CPZ,ADAM23,ADAM21,ADAM20,ADAM18,ADAM15,ADAM9,RPS6KA5,ECEL1,ADAMTS4,ADAMTS2,ADAMTS1,NPEPPS,NAALAD2,NAALADL1,DPP3,PSMD14,PGCP,STAMBP,ADAM28,COPS5,ADAM30,ADAM29,ADAMTS13,ADAMTS8,ADAMTS5,ADAMTS7,ADAMTS6,AGTPBP1,DNPEP,TRHDE,CPA4,AMZ2,YBEY,CNDP2,CPXM1,ADAMTS9,CPA6,RNPEPL1,ADAMTSL3,TMEM27,STAMBPL1,ACE2,PAPPA2,XPNPEP3,ERAP2,BRCC3,AGBL2,ERMP1,CNDP1,AGBL4,C9orf3,XRCC6BP1,CPA5,MYSM1,AGBL1,CPO,ZFP90,AMZ1,AQPEP,FOLH1B,AGBL3 |
| heme binding | 0.01 | 1 | AMBP,CAT,CBS,CBS,CYB5A,CYBA,CYBB,CYC1,CYP1A1,CYP1A2,CYP1B1,CYP2A6,CYP2A7,CYP3A7,CYP2A13,CYP2B6,CYP2C19,CYP2C8,CYP2C9,CYP2C18,CYP2D6,CYP2E1,CYP2F1,CYP2J2,CYP3A4,CYP3A5,CYP4A11,CYP4B1,CYP7A1,CYP8B1,CYP11A1,CYP11B1,CYP11B2,CYP17A1,CYP19A1,CYP21A2,CYP24A1,CYP26A1,CYP27A1,CYP27B1,CYP51A1,DOCK2,GUCY1A2,GUCY1A3,GUCY1B3,HBA2,HBM,HBB,HBD,HBE1,HBG1,HBG2,HBQ1,HBZ,HMOX1,IDO1,FADS1,FADS3,LPO,CYP4F3,MB,MPO,NOS1,NOS2,NOS3,PTGIS,PTGS1,PTGS2,SDHC,SDHD,SUOX,TBXAS1,TDO2,TPO,PXDN,EPX,CYP4F2,HERC2,FADS2,CYP7B1,PGRMC2,PGRMC1,CYP46A1,CYP4F8,EIF2AK1,CYP2S1,NENF,DUOX2,NOX4,HEBP1,CYB5R4,CYP39A1,DUOX1,CYCS,CYP2W1,CYP26B1,CYP20A1,CYP4F11,NGB,CYP3A43,CYP4F12,FA2H,NOX5,CYB5B,CYP2U1,CYGB,CYP2R1,CYB5D1,CYB5D2,CYP4F22,PXDNL,CYP4Z2P,IDO2,CYP4Z1,CYP4X1,CYP4A22,CYP4V2,CYP27C1,CYP26C1 |
| collagen | 0.01 | 1 | COL1A1,COL1A2,COL2A1,COL3A1,COL4A1,COL4A2,COL4A3,COL4A4,COL4A6,COL5A1,COL5A2,COL10A1,COL11A1,COL11A2,COL19A1,LOX,COL14A1,COL5A3,COL18A1,COL27A1,COL24A1 |
| acyl-CoA dehydrogenase activity | 0.02 | 1 | ACADM,ACADM,ACADS,ACADSB,ACOX1,ACOX2,ACOX3,ACAD8,ACAD9,ACOXL,ACAD10,ACAD11 |
| T cell activation | 0.02 | 1 | ADA,CBLB,CD2,CD3E,CD3G,CD7,CD8A,CD8B,CD80,CD86,CD48,DDOST,DPP4,FKBP1A,HSPD1,IFNAR1,IRF4,SMAD3,NCK1,PRLR,VAV1,WAS,NCK2,TNFSF14,KIF13B,ICOSLG,FOXP3,CLEC7A,TREML2,CD276,SLA2,HSH2D,NLRC3 |

The Magenta pathway analysis was based on the results from gene-based test which was run on Set 1 meta-analysis results.

a. Used the 95 percentile of all gene scores as enrichment cutoff.

**Supplementary Table 8. VEGAS-Pathway analysis results on meta of Asian samples.**

| GO_ID | GO_term | P[a] | Genes |
|---|---|---|---|
| GO:0030199 | collagen fibril organization | 3.8E-05 (0.17) | COL11A1,DPT,TGFB2,COL5A2,ADAMTS3,LOX,ADAMTS2,FOXC1,COL11A2,COL12A1,COL1A2,COL14A1,TGFBR1,LMX1B,COL5A1,SERPINH1,COL2A1,LUM,ANXA2,FOXC2,NF1,COL1A1,COL5A3 |
| GO:0030198 | extracellular matrix organization | 4.6E-05 (0.21) | VWA1,HSPG2,COL8A2,CYR61,COL11A1,DPT,TNR,LAMC1,ELF3,TGFB2,AGT,NID1,PXDN,MPV17,COL5A2,COL4A3,VHL,CCDC80,APBB2,PDGFRA,ADAMTS3,IBSP,C4orf31,EGFLAM,LOX,TGFBI,SPINK5,B4GALT7,ADAMTS2,FOXC1,C6orf15,TNXB,COL11A2,COL19A1,COL12A1,SERAC1,COL1A2,CSGALNACT1,TNFRSF11B,COL14A1,PTK2,B4GALT1,RECK,ECM2,TGFBR1,OLFML2A,LMX1B,POMT1,COL5A1,ITGA8,SPOCK2,KAZALD1,NFKB2,MUC5AC,ILK,WT1,HSD17B12,SERPINH1,MPZL3,APLP2,ADAMTS20,COL2A1,MYF5,DCN,POSTN,COL4A2,LGALS3,ANXA2,MYH11,GFOD2,CRISPLD2,FOXC2,VMO1,VTN,NF1,COL1A1,COL5A3,APLP1,MIA,BCL3,ERCC2,FKBP1A,CST3,MMP9,APP,COL18A1,COL6A2,TMPRSS6 |
| GO:0044420 | extracellular matrix part | 5.4E-05 (0.25) | VWA1,MFAP2,HSPG2,COL16A1,COL8A2,COL9A2,COL24A1,COL11A1,LAMC2,HMCN1,LAD1,LAMB3,USH2A,NID1,COL5A2,COL4A3,COL6A3,COLQ,COL7A1,DAG1,COL8A1,CCDC80,AMTN,SNCA,PRSS12,SLC1A3,EGFLAM,ERBB2IP,LOX,RELL2,SPARC,GABRA6,TNXB,COL11A2,VEGFA,TINAG,DST,COL9A1,COL12A1,LAMA4,COL10A1,LAMA2,SMOC2,COL28A1,VWC2,COL1A2,ACHE,LAMB4,COL14A1,FREM1,COL15A1,COL27A1,TNC,LAMC3,COL5A1,ENTPD2,COL13A1,MMRN2,COL17A1,SMC3,MUC5AC,EFEMP2,MFAP5,GRIN2B,COL2A1,LUM,NTN4,FGF9,FREM2,COL4A2,ANG,NID2,SMOC1,PAPLN,MFAP1,FBN1,ANXA2,CILP,SPN,NTN1,MFAP4,COL1A1,TIMP2,LAMA1,LAMA3,COL5A3,APLP1,LAMA5,COL9A3,ADAMTS1,TFF3,COL6A1,TIMP3 |
| GO:0060325 | face morphogenesis | 1.9E-04 (0.87) | CSRNP1,TIPARP,PDGFRA,ASPH,ARID5B,SGPL1,PLEKHA1,MMP2,COL1A1 |
| GO:0005201 | extracellular matrix structural constituent | 1.9E-04 (0.87) | WNT4,MATN1,TINAGL1,COL8A2,COL9A2,COL24A1,COL11A1,TUFT1,LAMC1,OPTC,WNT3A,PXDN,MATN3,EMILIN1,COL5A2,FN1,WNT6,COL4A3,FBLN2,IMPG2,MUC4,STATH,ENAM,MEPE,FBN2,COL11A2,COL9A1,COL12A1,IMPG1,LAMA4,ELN,TFPI2,COL1A2,MUC17,LAMB1,WNT2,WNT16,COL14A1,COL15A1,COL27A1,COL5A1,COL13A1,MUC5AC,EFEMP2,CD4,MFAP5,MGP,COL2A1,LUM,COL4A2,FBN1,ACAN,WNT9B,CHAD,EMILIN2,LAMA1,FBN3,COL5A3,COMP,COL9A3,COL18A1,COL6A2,FBLN1 |
| GO:0005801 | cis-Golgi network | 2.6E-04 (1) | TRAPPC3,PHTF1,GOLIM4,MAP6D1,FAM134B,HOOK3,SCYL1,TRAPPC4,DNM1L,COG3,SCFD1,TMED10,GOLGA5,TRAPPC1,GOSR1,COPZ2,KIAA1012,TRAPPC5 |
| GO:0031012 | extracellular matrix | 4.2E-04 (1) | VWA1,MFAP2,WNT4,MATN1,COL16A1,COL8A2,COL9A2,LEPRE1,PODN,COL24A1,F3,COL11A1,NTNG1,WNT2B,ADAMTSL4,RPTN,BCAN,ADAMTS4,DPT,TNR,LAMC2,HMCN1,LAD1,OPTC,LAMB3,USH2A,TGFB2,WNT3A,NID1,ZP4,PXDN,MATN3,EMILIN1,LTBP1,VIT,EFEMP1,FBLN7,COL5A2,FN1,WNT10A,COL4A3,COL6A3,GPC1,CHL1,TIMP4,WNT7A,COLQ,EFHB,CRTAP,COL7A1,DAG1,WNT5A,ADAMTS9,COL8A1,IMPG2,CCDC80,COL6A |

| | | | |
|---|---|---|---|
| | | | 6,MUC4,SPON2,CPZ,SOD3,ENAM,ADAMTS3,MEPE,SNCA,NPNT,PRSS12,C4orf31,SPOCK3,ADAMTS16,ADAMTS12,SLC1A3,EGFLAM,FGF10,ERBB2IP,THBS4,HAPLN1,LOX,FBN2,ADAMTS19,TGFBI,SPOCK1,WNT8A,RELL2,FGF1,SPARC,GABRA6,ADAMTS2,GPLD1,C6orf15,TNXB,COL11A2,VEGFA,CRISP3,TINAG,DST,COL9A1,COL12A1,IMPG1,LAMA4,COL10A1,LAMA2,CTGF,SERAC1,SMOC2,COL28A1,VWC2,ELN,ZP3,TFPI2,COL1A2,GPC2,EMID2,RELN,LAMB4,WNT2,WNT16,PTPRZ1,PRSS2,LPL,MMP16,MATN2,CTHRC1,NOV,COL14A1,OC90,FREM1,ADAMTSL1,MAMDC2,ECM2,COL15A1,COL27A1,TNC,OLFML2A,LAMC3,NTNG2,ADAMTSL2,COL5A1,ENTPD2,UCMA,RBP3,COL13A1,ADAMTS14,SPOCK2,SFTPD,MMRN2,CRTAC1,WNT8B,KAZALD1,COL17A1,SMC3,TECTB,FGFR2,MMP21,MUC5AC,MMP26,SPON1,NAV2,CD44,HSD17B12,ZP1,FLRT1,CD248,WNT11,MMP13,TECTA,ADAMTS15,WNT5B,VWF,MFAP5,GRIN2B,MGP,ADAMTS20,COL2A1,WNT1,MMP19,DCN,NTN4,MMP17,FGF9,POSTN,FREM2,GPC6,COL4A2,ANG,MMP14,COCH,NID2,BMP4,LGALS3,SMOC1,PAPLN,LTBP2,TGFB3,FLRT2,FBLN5,SERPINA1,THBS1,MFAP1,FBN1,ANXA2,CILP,THSD4,LOXL1,ADAMTS7,ADAMTSL3,HAPLN3,ADAMTS17,PCSK6,NTN3,MMP25,OTOA,SPN,PRSS36,MMP2,MMP15,GFOD2,ADAMTS18,CRISPLD2,NTN1,MFAP4,VTN,MMP28,WNT9B,CHAD,LGALS3BP,EMILIN2,LAMA1,LAMA3,ADAMTSL5,ADAMTS10,COL5A3,CALR,PODNL1,CILP2,APLP1,SPINT2,LTBP4,TGFB1,FLRT3,MMP24,EMILIN3,PI3,MMP9,BMP7,LAMA5,COL9A3,ADAMTS5,SOD1,TFF3,COL6A2,DGCR6,MMP11,TFIP11,EMID1,TIMP3,LGALS1,FBLN1 |
| GO:0060323 | head morphogenesis | 4.4E-04 (1) | FLVCR1,CSRNP1,TIPARP,PDGFRA,ASPH,ARID5B,SGPL1,PLEKHA1,MMP2,ANKRD11,COL1A1 |

This pathway analysis was based on the results from gene-based test which was run on Set 2 meta-analysis results.

b. Empirical P-value from 500,000 simulations. P-values after Bonferroni correction for multiple testing were included in the brackets.

**Supplementary Table 9. Top five pathways from VEGAS-Pathway analysis of meta on European and Asian samples.**

| GO_ID | GO_term | P[a] | Genes |
|---|---|---|---|
| GO:0030199 | collagen fibril organization | 3.2E-07 (1.5E-3) | COL11A1,DPT,TGFB2,COL5A2,ADAMTS3,LOX,ADAMTS2,FOXC1,COL11A2,COL12A1,COL1A2,COL14A1,TGFBR1,LMX1B,COL5A1,SERPINH1,COL2A1,LUM,ANXA2,FOXC2,NF1,COL1A1,COL5A3 |
| GO:0005581 | collagen | 3.5E-06 (0.016) | COL16A1,COL9A2,COL24A1,COL11A1,COL5A2,COL4A3,COL6A3,COL7A1,COL8A1,LOX,TNXB,COL11A2,COL9A1,COL12A1,COL10A1,COL1A2,COL14A1,COL15A1,COL27A1,COL5A1,COL13A1,COL2A1,LUM,COL4A2,COL1A1,COL5A3,COL9A3,COL6A1 |
| GO:0005583 | fibrillar collagen | 4.8E-06 (0.022) | COL11A1,COL5A2,TNXB,COL11A2,COL1A2,COL5A1,COL2A1,LUM,COL1A1,COL5A3 |
| GO:0044420 | extracellular matrix part | 5.2E-06 (0.024) | VWA1,MFAP2,HSPG2,COL16A1,COL8A2,COL9A2,COL24A1,COL11A1,LAMC2,HMCN1,LAD1,LAMB3,USH2A,NID1,COL5A2,COL4A3,COL6A3,COLQ,COL7A1,DAG1,COL8A1,CCDC80,AMTN,SNCA,PRSS12,SLC1A3,EGFLAM,ERBB2IP,LOX,RELL2,SPARC,GABRA6,TNXB,COL11A2,VEGFA,TINAG,DST,COL9A1,COL12A1,LAMA4,COL10A1,LAMA2,SMOC2,COL28A1,VWC2,COL1A2,ACHE,LAMB4,COL14A1,FREM1,COL15A1,COL27A1,TNC,LAMC3,COL5A1,ENTPD2,COL13A1,MMRN2,COL17A1,SMC3,MUC5AC,EFEMP2,MFAP5,GRIN2B,COL2A1,LUM,NTN4,FGF9,FREM2,COL4A2,ANG,NID2,SMOC1,PAPLN,MFAP1,FBN1,ANXA2,CILP,SPN,NTN1,MFAP4,COL1A1,TIMP2,LAMA1,LAMA3,COL5A3,APLP1,LAMA5,COL9A3,ADAMTS1,TFF3,COL6A1,TIMP3 |
| GO:0031012 | extracellular matrix | 1.3E-05 (0.06) | VWA1,MFAP2,WNT4,MATN1,COL16A1,COL8A2,COL9A2,LEPRE1,PODN,COL24A1,F3,COL11A1,NTNG1,WNT2B,ADAMTSL4,RPTN,BCAN,ADAMTS4,DPT,TNR,LAMC2,HMCN1,LAD1,OPTC,LAMB3,USH2A,TGFB2,WNT3A,NID1,ZP4,PXDN,MATN3,EMILIN1,LTBP1,VIT,EFEMP1,FBLN7,COL5A2,FN1,WNT10A,COL4A3,COL6A3,GPC1,CHL1,TIMP4,WNT7A,COLQ,EFHB,CRTAP,COL7A1,DAG1,WNT5A,ADAMTS9,COL8A1,IMPG2,CCDC80,COL6A6,MUC4,SPON2,CPZ,SOD3,ENAM,ADAMTS3,MEPE,SNCA,NPNT,PRSS12,C4orf31,SPOCK3,ADAMTS16,ADAMTS12,SLC1A3,EGFLAM,FGF10,ERBB2IP,THBS4,HAPLN1,LOX,FBN2,ADAMTS19,TGFBI,SPOCK1,WNT8A,RELL2,FGF1,SPARC,GABRA6,ADAMTS2,GPLD1,C6orf15,TNXB,COL11A2,VEGFA,CRISP3,TINAG,DST,COL9A1,COL12A1,IMPG1,LAMA4,COL10A1,LAMA2,CTGF,SERAC1,SMOC2,COL28A1,VWC2,ELN,ZP3,TFPI2,COL1A2,GPC2,EMID2,RELN,LAMB4,WNT2,WNT16,PTPRZ1,PRSS2,LPL,MMP16,MATN2,CTHRC1,NOV,COL14A1,OC90,FREM1,ADAMTSL1,MAMDC2,ECM2,COL15A1,COL27A1,TNC,OLFML2A,LAMC3,NTNG2,ADAMTSL2,COL5A1,ENTPD2,UCMA,RBP3,COL13A1,ADAMTS14,SPOCK2,SFTPD,MMRN2,CRTAC1,WNT8B,KAZALD1,COL17A1,SMC3,TECTB,FGFR2,MMP21,MUC5AC,MMP26,SPON1,NAV2,CD44,HSD17B12,ZP1,FLRT1,CD248,WNT11,MMP13,TECTA,ADAMTS15,WNT5B,VWF,MFAP5,GRIN2B,MGP,ADAMTS20,COL2A1,WNT1,MMP19,DCN,NTN4,MMP17,FGF9,POSTN,FREM2,GPC6,COL4A2,ANG,MMP14,COCH,NID2,BMP4,LGALS3,SMOC1,PAPLN,LTBP2,TGFB3,FLRT2,FBLN5,SERPINA1,THBS1,MFAP1,FBN1,ANXA2,CILP,THSD4,LOXL1,ADAMTS7,ADAMTSL3,HAPLN3,ADAMTS17,PCSK6,NTN3,MMP25,OTOA,SPN,PRSS36,MMP2,MMP15,G |

| | | | |
|---|---|---|---|
| | | | FOD2,ADAMTS18,CRISPLD2,NTN1,MFAP4,VTN,MMP28,WNT9B,CHAD,LGALS3BP,EMILIN2,LAMA1,LAMA3,ADAMTSL5,ADAMTS10,COL5A3,CALR,PODNL1,CILP2,APLP1,SPINT2,LTBP4,TGFB1,FLRT3,MMP24,EMILIN3,PI3,MMP9,BMP7,LAMA5,COL9A3,ADAMTS5,SOD1,TFF3,COL6A2,DGCR6,MMP11,TFIP11,EMID1,TIMP3,LGALS1,WNT7B |

These results were from the meta-analysis of pathways obtained from both European and Asian samples using Fisher's method.

c. Empirical P-value from 500,000 simulations. P-values after Bonferroni correction for multiple testing were included in the brackets.

**Supplementary Table 10. Key GO pathways suggested from GRAIL analysis of Table 2 Loci.**

| | |
|---|---|
| GO:0030020 | extracellular matrix structural constituent conferring tensile strength |
| GO:0005581 | collagen |
| GO:0006875 | metal ion homeostasis |
| GO:0030003 | cation homeostasis |
| GO:0006873 | cell ion homeostasis |
| GO:0050801 | ion homeostasis |
| GO:0006817 | phosphate transport |
| GO:0005201 | extracellular matrix structural constituent |
| GO:0044420 | extracellular matrix part |
| GO:0019725 | cell homeostasis |
| GO:0015698 | inorganic anion transport |
| GO:0006820 | anion transport |
| GO:0005918 | septate junction |
| GO:0042592 | homeostasis |
| GO:0048522 | positive regulation of cellular process |
| GO:0006874 | calcium ion homeostasis |
| GO:0042127 | regulation of cell proliferation |
| GO:0048598 | embryonic morphogenesis |
| GO:0003707 | steroid hormone receptor activity |
| GO:0008283 | cell proliferation |

**Supplementary Table 11. Association between CCT loci and keratoconus risk in two independent studies.**

| Locus[a] | Chr | Leading SNP or its proxy ($r^2$)[b] | A1/A2 | South Australia samples[c] (N case/con=652/2,761) | | | | | US samples[c] (N case/con=222/3,324) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | AF1case | AF1con | OR | Se | P | AF1case | AF1con | OR | Se | P |
| *COL8A2* | 1 | rs96067 | A/G | 0.78 | 0.80 | 0.86 | 0.07 | 0.04 | 0.80 | 0.80 | 1.10 | 0.13 | 0.45 |
| ***COL4A3*** | 2 | rs7606754 | A/G | 0.37 | 0.33 | 1.19 | 0.06 | 6.0E-03 | Na | Na | Na | Na | Na |
| | | rs7560053 (0.8) | T/C | | | | | | 0.34 | 0.34 | 0.96 | 0.11 | 0.71 |
| ***FNDC3B*** | 3 | rs4894535 | T/C | 0.21 | 0.16 | 1.46 | 0.08 | 1.3E-06 | 0.21 | 0.15 | 1.52 | 0.13 | 8.5E-04 |
| ***TBL1XR1-KCNMB2*** | 3 | rs7620503 | T/C | Na | Na | Na | Na | Na | Na | Na | Na | Na | Na |
| ***NR3C2*** | 4 | rs3931397 | T/G | 0.09 | 0.08 | 1.22 | 0.11 | 0.07 | 0.10 | 0.08 | 1.15 | 0.17 | 0.41 |
| ***ADAMTS6*** | 5 | rs2307121 | T/C | 0.33 | 0.33 | 1.00 | 0.07 | 0.97 | 0.33 | 0.32 | 1.03 | 0.11 | 0.79 |
| *FAM46A-IBTK* | 6 | rs1538138 | T/C | 0.26 | 0.23 | 1.13 | 0.07 | 0.10 | 0.23 | 0.25 | 0.88 | 0.12 | 0.29 |
| ***VKORC1L1*** | 7 | rs11763147 | A/G | Na | Na | Na | Na | Na | 0.44 | 0.42 | 1.22 | 0.10 | 0.06 |
| *C7orf42* | 7 | rs4718428 | T/G | Na | Na | Na | Na | Na | 0.28 | 0.29 | 0.78 | 0.12 | 0.03 |
| *MPDZ-NF1B* | 9 | rs1324183 | A/C | 0.24 | 0.20 | 1.33 | 0.07 | 8.8E-05 | 0.26 | 0.21 | 1.33 | 0.12 | 0.02 |
| ***LPAR1*** | 9 | rs1007000 | T/C | 0.20 | 0.22 | 0.91 | 0.08 | 0.24 | 0.19 | 0.21 | 0.83 | 0.13 | 0.17 |
| *RXRA-COL5A1* | 9 | rs1536482 | A/G | 0.40 | 0.34 | 1.32 | 0.06 | 1.2E-05 | 0.41 | 0.33 | 1.32 | 0.10 | 6.5E-03 |
| *COL5A1* | 9 | rs7044529 | T/C | 0.18 | 0.14 | 1.34 | 0.08 | 3.0E-04 | 0.17 | 0.14 | 1.44 | 0.14 | 7.4E-03 |
| ***PTGDS*** | 9 | rs11145951 | T/C | 0.45 | 0.49 | 0.87 | 0.06 | 0.03 | 0.45 | 0.48 | 0.84 | 0.10 | 0.09 |
| ***ARID5B*** | 10 | rs7090871 | T/C | 0.58 | 0.58 | 1.00 | 0.06 | 1.00 | 0.66 | 0.61 | 1.21 | 0.11 | 0.07 |
| ***ARHGAP20-POU2AF1*** | 11 | rs4938174 | A/G | 0.29 | 0.30 | 0.95 | 0.07 | 0.43 | 0.27 | 0.31 | 0.76 | 0.11 | 0.02 |
| ***Near GLT8D2 (5')*** | 12 | rs1564892 | A/G | Na | Na | Na | Na | Na | Na | Na | Na | Na | Na |
| *FGF9-SGCG* | 13 | rs1034200 | A/C | 0.30 | 0.28 | 1.07 | 0.07 | 0.34 | Na | Na | Na | Na | Na |
| | | rs1034198 (1) | T/C | | | | | | 0.23 | 0.28 | 0.80 | 0.12 | 0.07 |
| *Near FOXO1(3')* | 13 | rs2721051 | T/C | 0.14 | 0.10 | 1.53 | 0.09 | 3.2E-06 | 0.17 | 0.10 | 1.83 | 0.14 | 9.5E-06 |
| ***Near TJP1(5')*** | 15 | rs785422 | T/C | 0.09 | 0.10 | 0.87 | 0.11 | 0.18 | 0.11 | 0.11 | 1.09 | 0.16 | 0.60 |
| ***SMAD3*** | 15 | rs12913547 | T/C | 0.81 | 0.79 | 1.18 | 0.08 | 0.03 | Na | Na | Na | Na | Na |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | rs4601989 (0.67) | C/T | | | | | | 0.24 | 0.20 | 1.38 | 0.13 | 0.01 |
| *Near AKAP13 (5')* | 15 | rs6496932 | A/C | Na | Na | Na | Na | Na | 0.23 | 0.20 | 1.06 | 0.12 | 0.63 |
| *LRRK1* | 15 | rs930847 | T/G | 0.77 | 0.78 | 0.96 | 0.07 | 0.55 | Na | Na | Na | Na | Na |
| *CHSY1* | 15 | rs752092 | A/G | 0.67 | 0.67 | 0.98 | 0.07 | 0.82 | Na | Na | Na | Na | Na |
| | | rs8043243 (0.9) | C/T | | | | | | 0.38 | 0.34 | 1.23 | 0.11 | 0.06 |
| *BANP-ZNF469* | 16 | rs9938149 | A/C | 0.68 | 0.64 | 1.19 | 0.07 | 7.1E-03 | 0.33 | 0.27 | 1.52 | 0.14 | 2.5E-3 |
| ***HS3ST3B1-PMP22*** | 17 | rs12940030 | T/C | 0.71 | 0.71 | 0.99 | 0.07 | 0.92 | Na | Na | Na | Na | Na |
| | | rs2323457 (1) | C/A | | | | | | 0.29 | 0.29 | 1.12 | 0.11 | 0.31 |

a. Locus assigned to the RefSeq protein-coding gene within or near (noted near) the association signal interval (defined by linkage disequilibrium plot using a measure r2 > 0.9 with the leading SNP implemented in SNAP using the CEU reference). The locus was assigned to the interval defined by the two flanking RefSeq protein-coding genes if clearly intergenic. All novel loci for both European and Asian populations are marked in bold. The locus *COL4A3* was suggested in a set of Croatian samples but that had not reached statistical significance. The locus *MPDZ-NF1B* was previously reported as 9p23. The locus *FGF9-SGCG* was previously reported as *AVGR8*.

b. For the SNPs not genotyped in the US samples, we presented the results from its proxy.

c. Na's in results indicate that the SNP is not genotyped.

**Supplementary Table 12. Association between CCT loci and susceptibility to primary open angle glaucoma in three independent studies.**

| | | | | GLAUGEN + NEIGHBOR HTG[b] (Ncase/con=1669/3443) | | | GLAUGEN + NEIGHBOR NTG[b] (Ncase/con=720/3443) | | | SouthAustralia (Ncase/con=590/3,956) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Locus[a]** | **Chr** | **Leading SNP** | **A1/A2** | **OR** | **Se** | **P** | **OR** | **Se** | **P** | **OR** | **Se** | **P** |
| *COL8A2* | 1 | rs96067 | A/G | 0.88 | 0.09 | 0.05 | 1.03 | 0.12 | 0.77 | 1.08 | 0.08 | 0.36 |
| ***COL4A3*** | 2 | rs7606754 | A/G | 0.96 | 0.07 | 0.47 | 1.04 | 0.10 | 0.63 | 1.02 | 0.07 | 0.79 |
| ***FNDC3B*** | 3 | rs4894535 | T/C | 0.81 | 0.10 | 6.9E-03 | 0.71 | 0.14 | 1.4E-03 | 0.85 | 0.09 | 0.08 |
| ***TBL1XR1-KCNMB2*** | 3 | rs7620503 | T/C | 0.91 | 0.07 | 0.10 | 0.94 | 0.10 | 0.41 | 0.83 | 0.07 | 0.01 |
| ***NR3C2*** | 4 | rs3931397 | T/G | 0.89 | 0.13 | 0.23 | 0.81 | 0.19 | 0.10 | 0.95 | 0.13 | 0.69 |
| ***ADAMTS6*** | 5 | rs2307121 | T/C | 0.94 | 0.08 | 0.27 | 0.94 | 0.10 | 0.39 | 0.92 | 0.07 | 0.19 |
| *FAM46A-IBTK* | 6 | rs1538138 | T/C | 0.92 | 0.08 | 0.18 | 0.98 | 0.11 | 0.79 | 1.02 | 0.07 | 0.75 |
| ***VKORC1L1*** | 7 | rs11763147 | A/G | 1.03 | 0.07 | 0.61 | 1.04 | 0.10 | 0.63 | Na | Na | Na |
| *C7orf42* | 7 | rs4718428 | T/G | 0.97 | 0.07 | 0.72 | 1.11 | 0.10 | 0.30 | 1.12 | 0.07 | 0.10 |
| *MPDZ-NF1B* | 9 | rs1324183 | A/C | 1.10 | 0.09 | 0.15 | 1.14 | 0.12 | 0.13 | 1.03 | 0.08 | 0.68 |
| ***LPAR1*** | 9 | rs1007000 | T/C | 1.01 | 0.09 | 0.91 | 1.05 | 0.11 | 0.52 | 0.91 | 0.08 | 0.26 |
| *RXRA-COL5A1* | 9 | rs1536482 | A/G | 1.08 | 0.07 | 0.17 | 0.96 | 0.10 | 0.59 | 0.92 | 0.09 | 0.35 |
| *COL5A1* | 9 | rs7044529 | T/C | 0.94 | 0.10 | 0.41 | 1.23 | 0.14 | 0.04 | 0.98 | 0.09 | 0.82 |
| ***LCN12-PTGDS*** | 9 | rs11145951 | T/C | 1.02 | 0.07 | 0.74 | 1.02 | 0.10 | 0.83 | 1.04 | 0.08 | 0.57 |
| ***ARID5B*** | 10 | rs7090871 | T/C | 0.94 | 0.07 | 0.24 | 1.02 | 0.10 | 0.79 | 1.08 | 0.08 | 0.31 |
| ***ARHGAP20-POU2AF1*** | 11 | rs4938174 | A/G | 0.93 | 0.08 | 0.23 | 0.95 | 0.11 | 0.47 | 0.82 | 0.07 | 6.4E-03 |
| ***Near GLT8D2 (5')*** | 12 | rs1564892 | A/G | Na | Na | Na | Na | Na | Na | 1.24 | 0.08 | 5.9E-03 |
| *FGF9-SGCG* | 13 | rs1034200 | A/C | 1.03 | 0.08 | 0.67 | 0.90 | 0.11 | 0.20 | 0.98 | 0.07 | 0.82 |
| *Near FOXO1(3')* | 13 | rs2721051 | T/C | 1.05 | 0.12 | 0.57 | 1.10 | 0.15 | 0.41 | 1.14 | 0.10 | 0.18 |
| ***Near TJP1(5')*** | 15 | rs785422 | T/C | 1.18 | 0.12 | 0.29 | 0.92 | 0.16 | 0.67 | 0.98 | 0.10 | 0.88 |
| ***SMAD3*** | 15 | rs12913547 | T/C | 1.05 | 0.08 | 0.46 | 0.89 | 0.12 | 0.19 | 1.00 | 0.08 | 0.97 |
| *Near AKAP13 (5')* | 15 | rs6496932 | A/C | 1.00 | 0.09 | 0.97 | 1.00 | 0.12 | 0.99 | 0.92 | 0.08 | 0.33 |
| *LRRK1* | 15 | rs930847 | T/G | 1.05 | 0.08 | 0.40 | 0.91 | 0.11 | 0.24 | 0.97 | 0.07 | 0.71 |
| *CHSY1* | 15 | rs752092 | A/G | 1.04 | 0.07 | 0.47 | 0.97 | 0.10 | 0.69 | 1.06 | 0.07 | 0.38 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *BANP-ZNF469* | 16 | rs9938149 | A/C | 1.00 | 0.07 | 0.96 | 1.02 | 0.10 | 0.74 | Na | Na | Na |
| ***HS3ST3B1-PMP22*** | 17 | rs12940030 | T/C | 0.98 | 0.08 | 0.77 | 1.04 | 0.10 | 0.57 | 1.08 | 0.07 | 0.26 |

a. Locus assigned to the RefSeq protein-coding gene within or near (noted near) the association signal interval (defined by linkage disequilibrium plot using a measure r2 > 0.9 with the leading SNP implemented in SNAP using the CEU reference). The locus was assigned to the interval defined by the two flanking RefSeq protein-coding genes if clearly intergenic. All novel loci for both European and Asian populations are marked in bold. The locus *COL4A3* was suggested in a set of Croatian samples but that had not reached statistical significance. The locus *MPDZ-NF1B* was previously reported as 9p23. The locus *FGF9-SGCG* was previously reported as *AVGR8*.

b. “HTG” stands for high-tension glaucoma and “NTG” stands for normal-tension glaucoma.

**Supplementary Table 13: Human and mouse corneal gene expression of CCT-associated loci.**

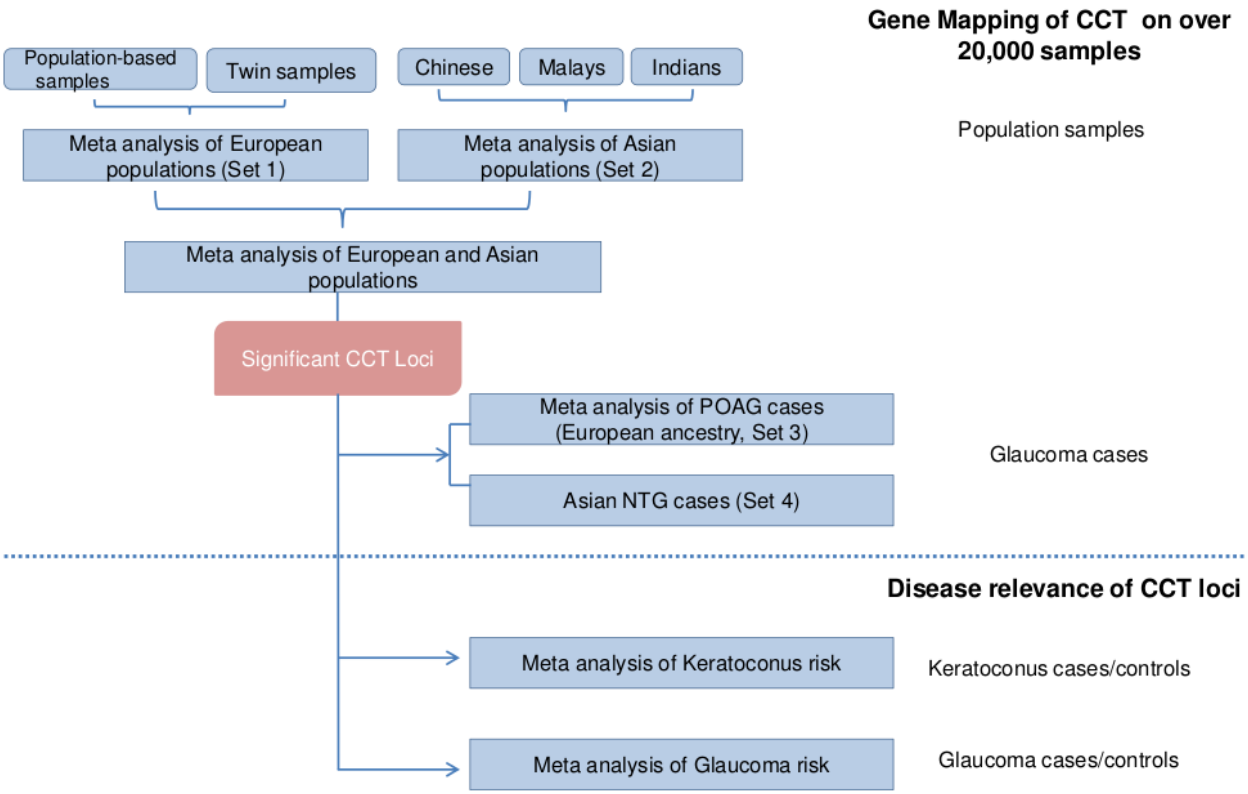
| Locus[a] | Expressed in human[b] | Expression Value[c] | Affymetrix Probe ID | Mouse homolog[d] | Expressed in mouse[b] | Expression Value[e] | Affymetrix Probe ID |
|---|---|---|---|---|---|---|---|
| USP37 | P | 6.5 | 226729_at | | P | 8.0 | 1438212_at |
| GPR15 | A | 4.3 | 208524_at | | A | 3.3 | 1431296_at |
| CWC27 | P | 7.4 | 223337_at | Sdccag10 | P | 8.5 | 1426455_at |
| ADAMTS6 | A | 3.1 | 220866_at | | A | 3.9 | 1437506_at |
| RXRA | P | 7.0 | 202426_s_at | | P | 6.0 | 1425762_a_at |
| COL5A1 | P | 5.7 | 203325_s_at | | P | 9.3 | 1434479_at |
| LCN12 | A | 4.3 | 230717_at | | A | 4.8 | 1429935_at |
| PTGDS | P | 13.2 | 212187_x_at | | P | 8.2 | 1423859_a_at |
| FGF9 | P | 6.8 | 206404_at | | P | 6.5 | 1420795_at |
| FOXO1 | P | 7.8 | 202723_s_at | | P | 9.4 | 1416982_at |
| TJP1 | P | 10.1 | 202011_at | | P | 12.0 | 1417749_a_at |
| AKAP13 | P | 7.2 | 227039_at | | P | 8.2 | 1440392_at |
| LRRK1 | P | 7.0 | 219441_s_at | | P | 9.4 | 1451985_at |
| CHSY1 | P | 9.9 | 203044_at | | P | 10.3 | 1434316_at |
| ZNF469 | P | 6.3 | 230440_at | Gm22 | P | 6.8 | 1459622_at |
| HS3ST3B1 | A | 4.2 | 1561908_a_at | | P | 5.7 | 1421331_at |
| COL8A2 | P | 8.6 | 221900_at | | P | 11.2 | 1434667_at |
| COL4A3 | A | 4.6 | 216898_s_at | | P | 8.4 | 1450224_at |
| FNDC3B | P | 5.5 | 242029_at | | P | 9.3 | 1452783_at |
| TBL1XR1 | P | 7.7 | 221428_s_at | | P | 7.6 | 1450739_at |
| KCNMB2 | P | 6.1 | 221097_s_at | | A | 3.6 | 1426322_a_at |
| NR3C2 | P | 7.7 | 205259_at | | P | 5.5 | 1435991_at |
| FAM46A | P | 7.5 | 224973_at | | P | 10.2 | 1437868_at |
| IBTK | P | 10.1 | 210970_s_at | | P | 5.8 | 1434282_at |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| VKORC1L1 | P | 7.6 | 224881_at | | P | 10.5 | 1429092_at |
| C7orf42 | P | 9.5 | 218008_at | 0610007L01Rik | P | 9.9 | 1428544_at |
| LPAR1 | P | 6.6 | 204038_s_at | | P | 9.8 | 1448606_at |
| ARID5B | P | 6.4 | 235404_at | | P | 7.3 | 1442176_at |
| ARHGAP20 | P | 5.3 | 1555020_a_at | | P | 5.7 | 1429918_at |
| GLT8D2 | P | 7.7 | 227070_at | | P | 7.8 | 1429402_at |
| SMAD3 | P | 6.8 | 205397_x_at | | P | 6.3 | 1450472_s_at |

Microarray was performed on corneas from two human donor samples (GSE29402) and three adult inbred strains of mice (C57BLKS/J, C57BL/6J, and SJL/J; GSE14270) using Affymetrix U133 plus 2.0 human expression arrays and Affymetrix GeneChip Mouse Genome 430 2.0 Arrays, respectively. Data ($log_2$ transformed) is shown for one representative probe in cases where there were multiple probes. A subset of these genes (*i.e.*, PTGDS and HS3ST3B1, TBL1XR1 and ARID5B) was retested with quantitative PCR to validate the mouse microarray expression. In all cases, the results were consistent.

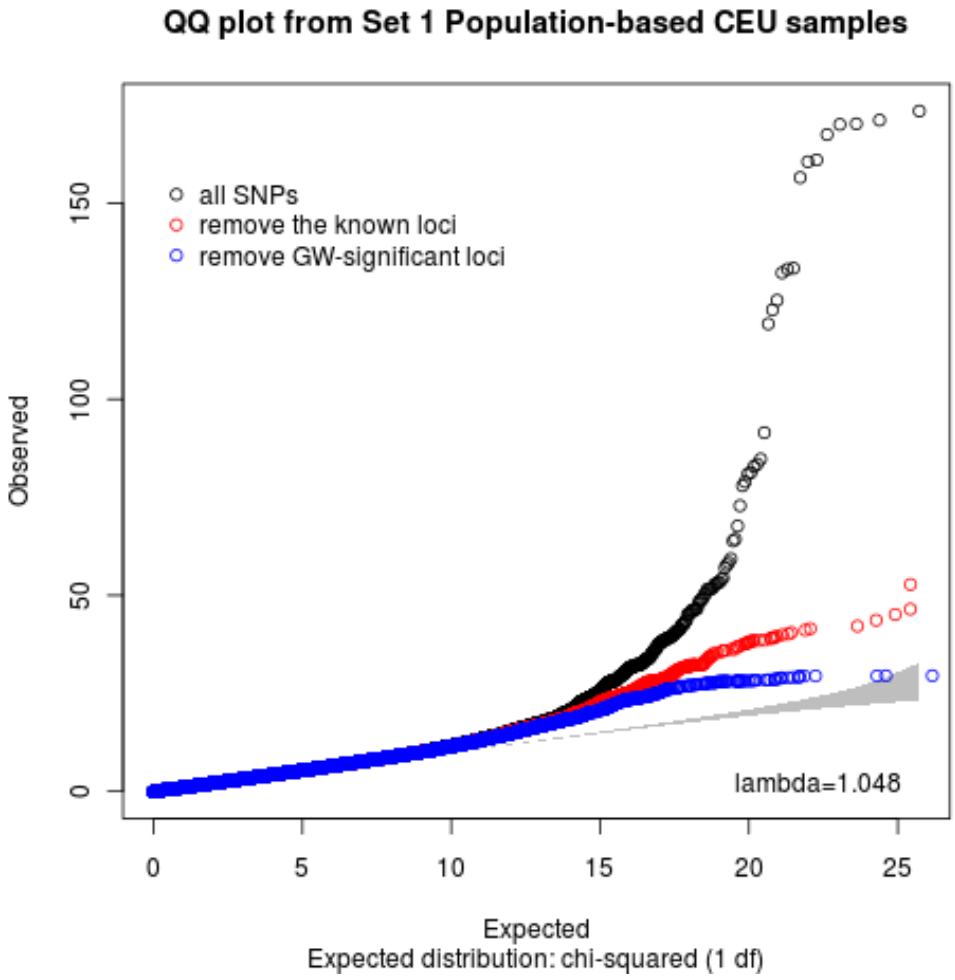
a. Boxed loci indicate loci where the leading SNP was intergenic.
b. Expression is summarized as absent (A) or present (P) based on expression greater than 5.0.
c. Expression value is the average of the two human samples.
d. Mouse homolog is the gene name used for the associated Affymetrix probe.
e. Expression value is the average of the C57BL/6J samples.

## Supplementary Figures:



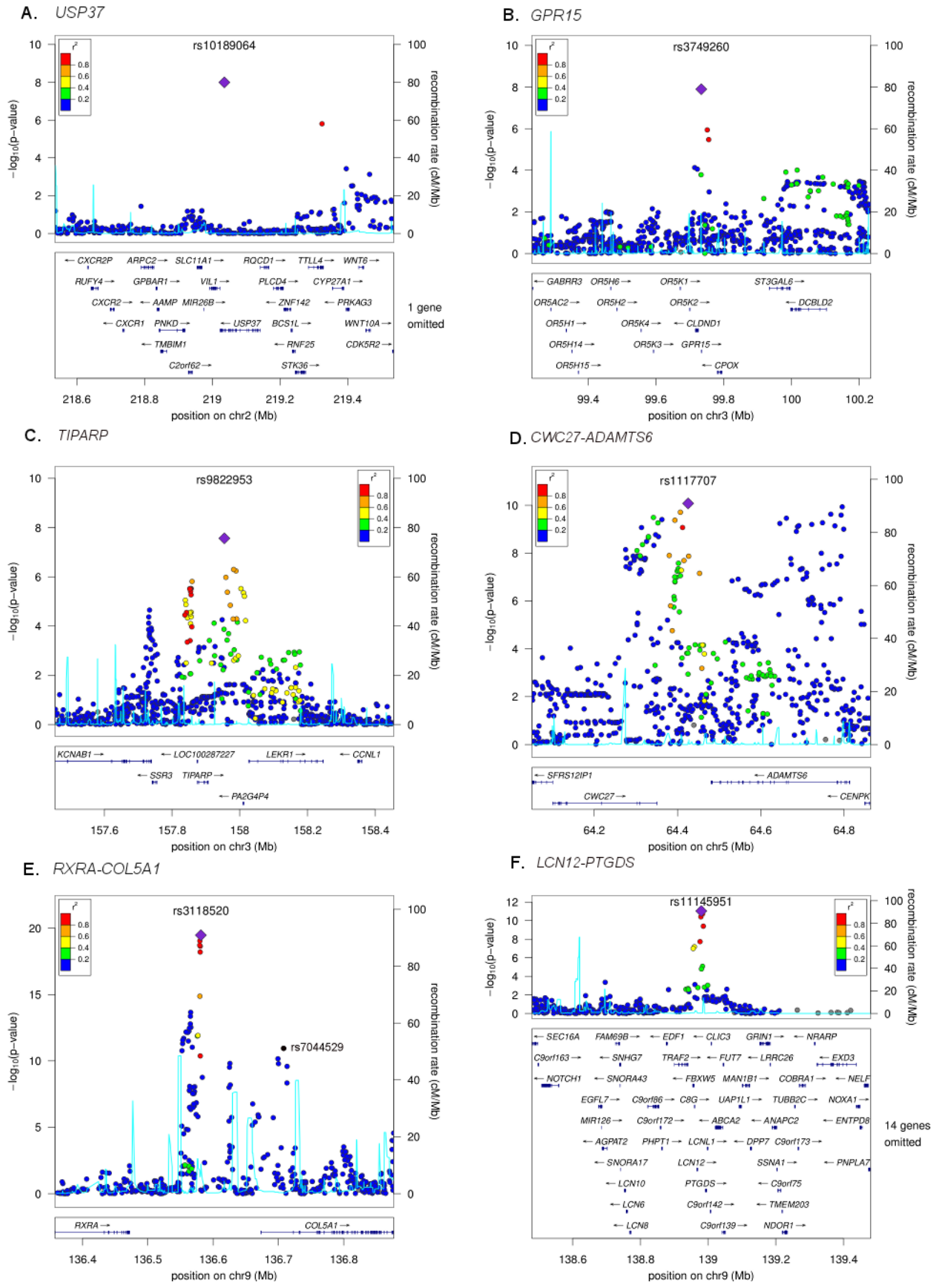

Supplementary Figure 1. Overall study design.

We conducted a large meta-analysis of GWASs on CCT from over 20,000 individuals, including individuals of European and Asian descent, affected and unaffected with glaucoma. According to these attributes, the study samples with CCT phenotypes were divided into four sets (Set 1-4). We conducted meta-analyses within each set, and to enhance the power we conducted a further meta-analysis combining the first two sets (European and Asian samples unaffected with eye disease). We then tested the significant loci obtained from the trans-ethnic meta-analysis in the sets of glaucoma patients, in order to determine whether the CCT loci identified in the general population also influence the slightly reduced CCT values in the glaucoma patients. Finally, we tested the significant CCT loci for association with keratoconus and glaucoma risk in the disease cohorts, in order to evaluate the potential clinical relevance of the CCT loci.

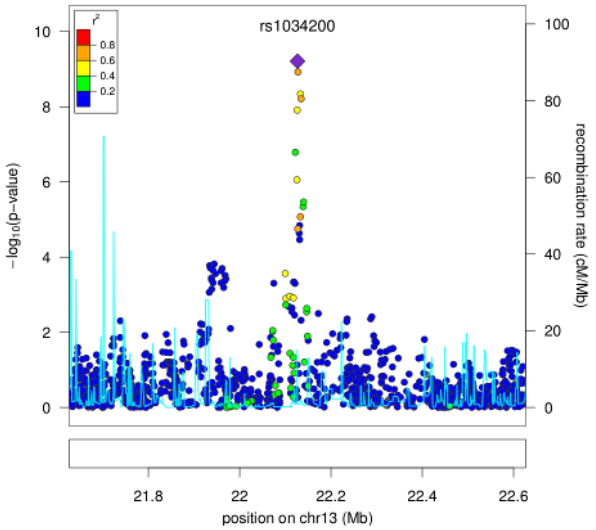



Supplementary Figure 2. Q-Q plot of meta-analysis on Set 1 samples.

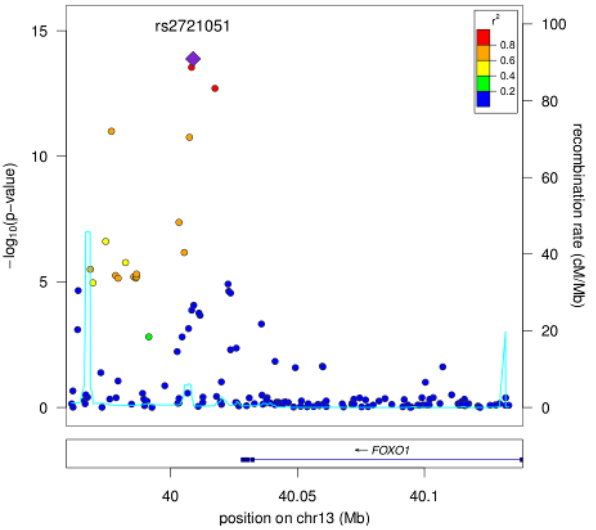
The observed test statistics is plotted against the expected test statistics. The black line includes all SNP, the red line removes the known CCT-associated loci, and the blue line further removes the genome-wide significant loci we identified in Table 1. The genomic control parameter is shown as “lambda” in the plot.


A. USP37
rs10189064
1 gene omitted
position on chr2 (Mb)
B. GPR15
rs3749260
position on chr3 (Mb)
C. TIPARP
rs9822953
position on chr3 (Mb)
D. CWC27-ADAMTS6
rs1117707
position on chr5 (Mb)
E. RXRA-COL5A1
rs3118520
rs7044529
position on chr9 (Mb)
F. LCN12-PTGDS
rs11145951
14 genes omitted
position on chr9 (Mb)
recombination rate (cM/Mb)

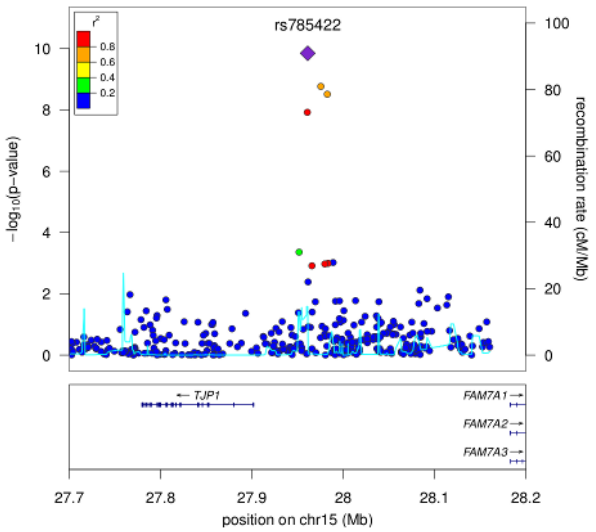
G. *FGF9-SGCG*



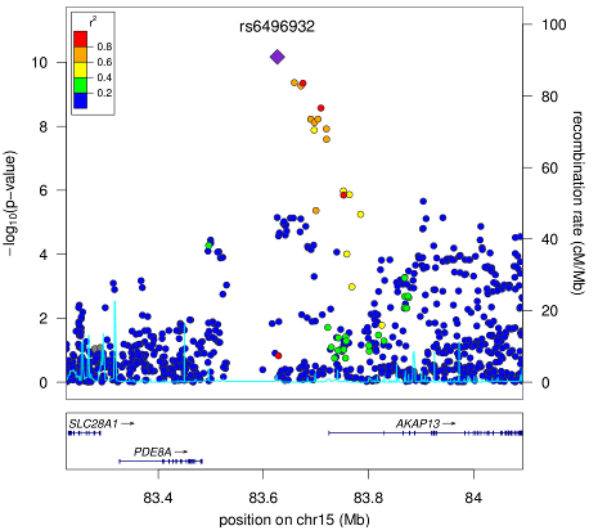

H. *FOXO1*



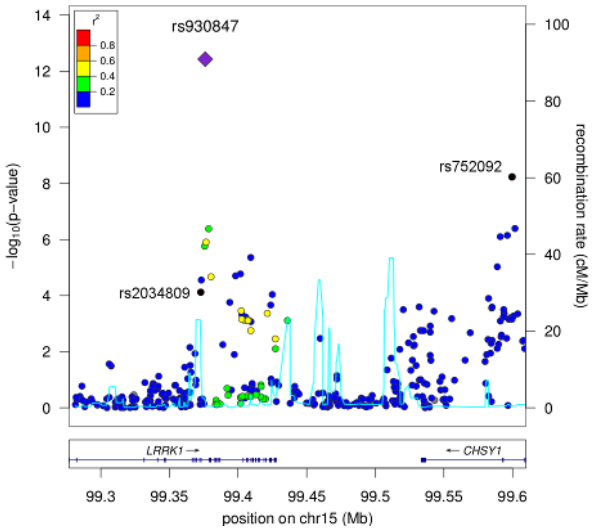

I. *TJP1*



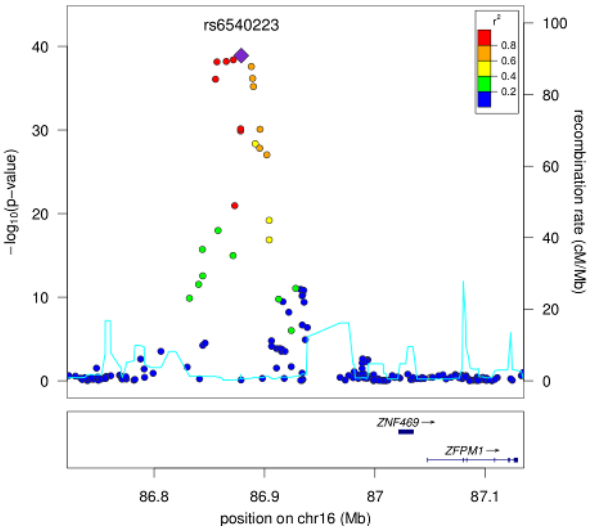

J. *AKAP13*

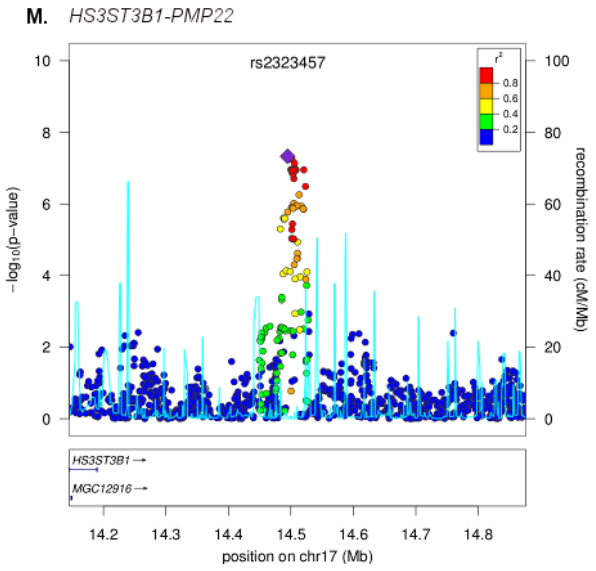



K. *LRRK1-CHSY1*



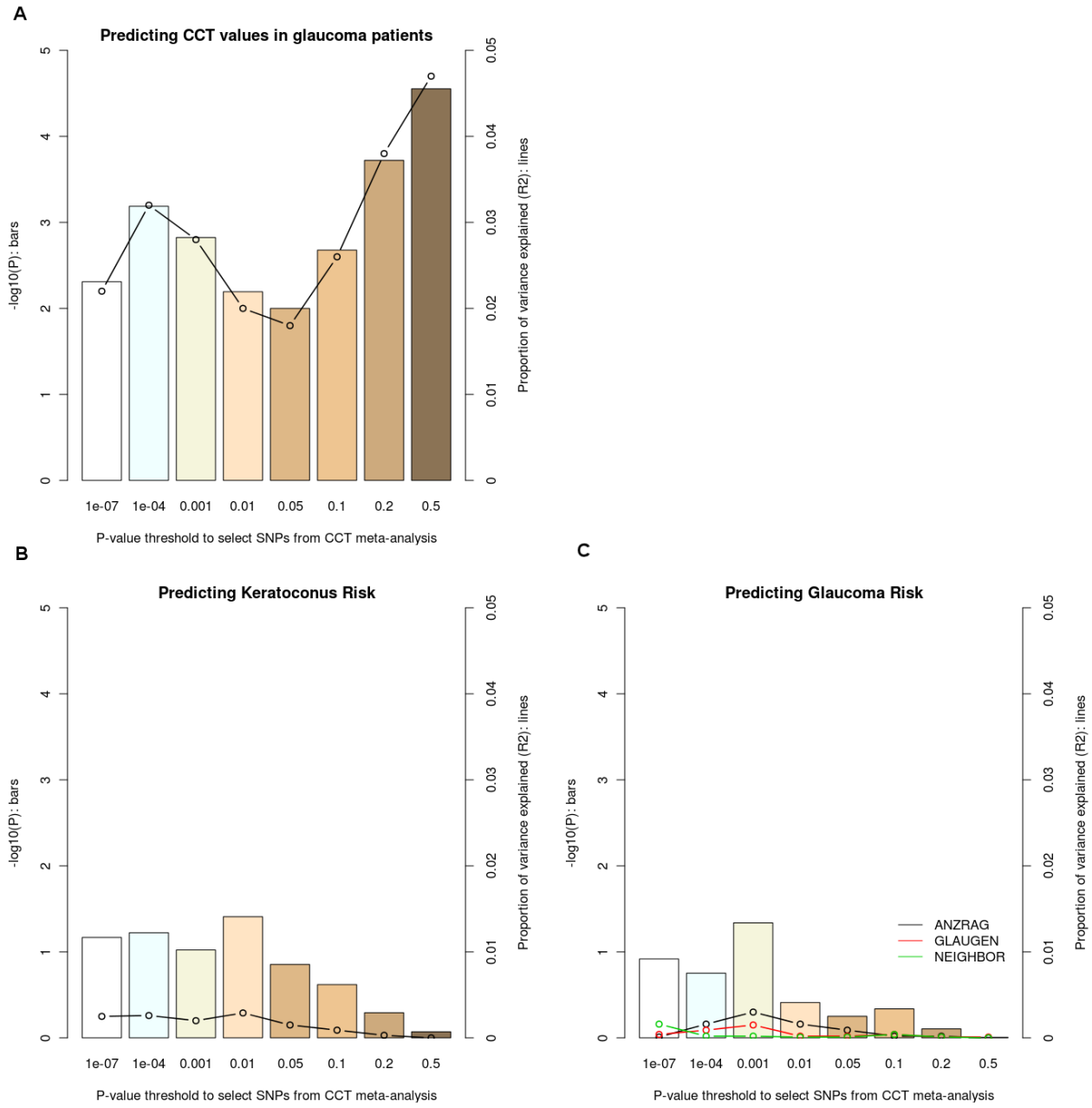

L. *ZNF469*






Supplementary Figure 3 A-M. Regional plots of CCT associated loci in Table 1.

The plots were generated using LocusZoom[1] (URL:http://csg.sph.umich.edu/locuszoom/).




Supplementary Figure 4 A-C. Polygenic modeling with CCT meta-analysis results as discovery set. (A) CCT of 363 POAG patients in the ANZRAG study as target set. (B) US Keratoconus case-control set (222 cases and 3324 controls) as target; (C). Three glaucoma case-control sets (ANZRAG, GLAUGEN and NEIGHBOR) as target. The bars represent the -log10 p-value from the prediction model (-log10 p-value from meta-analysis of the three sets in (C)), and the lines represent the proportion of phenotypic variance explained.

## Supplementary Notes:

### Study descriptions

#### *Lu et al. (2010)[2]:*

**Datasets/Samples.** This published study contained four main datasets from Australia and the United Kingdom. The AU twin cohort consisted of two sub-samples, 953 individuals from the Brisbane Adolescent Twin Study (BATS) and 761 individuals from the Twin Eye Study in Tasmania (TEST), making up a whole cohort of 1714 participants from 786 families. Twins from the UK were a sub-sample from the cohorts collected at St Thomas' Hospital in London. 1759 people from 1119 families were included in this study. The remaining two cohorts were genotyped on pooled samples from singletons with extreme CCT values. Blue Mountains Eye Study (BMES) used DNA pooling technique, namely BMES DNA pools and Adelaide study used blood pooling technique, namely Adelaide blood pools. All the datasets were mainly comprised of individuals with Northern European ancestries. Details of the cohorts are given in Lu et al (2010)[2].

**Phenotypes.** CCT was measured in these cohorts using ultrasound pachymetry and recorded for both eyes. Measurements were performed using a Tomey SP 2000 (Tomey Corp., Nagoya, Japan) in the Australian twin study and two pooling studies, and a DGH Technology (model 500; Scarsdale, NY) pachymeter in UK twin cohorts. Twin pairs were measured at the same time of day to avoid bias related to diurnal variation. The mean CCT value of both eyes was used throughout as the measurement. Mean, standard deviation (sd), range of CCT and age were provided in Supplementary Table 1, together with the proportion of females in the total dataset.

**Genotyping & Imputation.** All of these datasets were genotyped using commercial genotyping platforms (Supplementary Table 1). Similar quality control (QC) were applied to the AU and UK twin study, including minor allele frequency (MAF)≥1%, p-value for Hardy-Weinberg equilibrium test≥$10^{-6}$ for AU twin study for $10^{-4}$ UK twin study, SNP call rate>95% or Illumina Beadstudio GenCall score≥0.7. QCs applied to the pooling studies included: more than 5 probes in each pool; with a MAF greater than 1%; without a significant variance difference between case and control pools (i.e., the $\log_{10}$ transformed p-values from an F test on the ratio of case control pool variances were smaller than 6).
The imputation for the AU and UK twin samples were undertaken with reference to HapMap release 22 CEU using MACH and IMPUTE version 2 respectively. Each of the imputed datasets contains up to 2.4 million SNPs.

**Analysis.** Both AU and UK twin cohorts consist of either twin pairs or their close relatives (parents, siblings) in the family. We conducted the association test (--fastassoc) in MERLIN. The AU twin study was controlled for both age and gender effects, whilst the predominantly female UK samples were only controlled for age effects. The trait distribution of CCT was standardised. Two population-based cohorts were studied in the case-control pool design. The DNA or blood samples among the thick CCT group (upper 20% of the CCT distribution) were constructed as control pool, whereas samples among the thin CCT group (lower 20% of the CCT distribution) were constructed as case pool. We constructed the test statistics to take account of the pooling errors and assess the significance of allele frequency differences between the case/control pools. The pooled sample findings were validated by individual genotyping most of the pooled samples and additional samples.

#### *Vitart et al (2010)[3]:*

**Datasets/Samples**. The four populations (CROATIA-Vis, CROATIA-Korčula, CROATIA-Split, ORCADES) comprise healthy adult volunteers from the Croatian islands of Vis and Korčula, the Croatian urban city of Split and the northern isles of Orkney (Orkney Complex Disease Study, ORCADES, Scotland, UK). The studies received approval from relevant ethics committees in Scotland and Croatia and followed the tenets of the Declaration of Helsinki. Briefly, the Vis study included unselected adult participants, aged 18–93 years (mean = 56), a subset of which (N=640)

underwent a complete eye examination in summer 2007 and provided their ophthalmologic history. The Korčula study included a total of 969 examinees, aged 18-98 (mean=56.3), and most (N=930) underwent a complete eye examination. ORCADES is a family-based, cross-sectional study in the Scottish archipelago of Orkney. Among 1,285 individuals with eye measurements, only 529 (aged 22-88 (mean=55.1)) had been genotyped at the time of analysis. The Split study is a cross-sectional population study in the Croatian city of Split in which 499 individuals with whole-genome scans were available, aged 18-85 (mean=49.04), 372 of whom had undergone a complete eye examination.

**Phenotypes.** Central corneal thickness (CCT) was recorded along with other ocular biometric measurements using a Nidek Echoscan US-1800 A-scan device in all three Croatian studies after application of sterile oxybuprocaine anaesthetic eye drops (Minims-Chauvin Pharmaceuticals Ltd). The Orkney measurements were performed using an IOPac ultrasound pachymeter (POD; Heidelberg engineering). Measures on eyes with a history of trauma, intra-ocular surgery or LASIK operations were removed. Right eye values were plotted against the left eye values. Pearson correlations for right and left eyes were highly statistically significant for CCT (2-tailed significance level of 0.01): 0.9 Korčula and Vis, 0.92 for Split, 0.97 for ORCADES. Given the high correlations between right and left eye measures, the analysis was done on the right eye measures, unless the left eye had more complete measurements (e.g. due to trauma or cataract surgery on the right eye).

**Genotyping & Imputation.** Genotypes were generated using a dense Illumina SNP array, HumanHap 300v1 for Vis, a mix of HumanHap 300v2 and 370CNV-Quad for ORCADES, 370CNV-Quad for Korčula, and 370CNV-Quadv3 for Split, following the manufacturer's standard recommendations. Genotypes were determined using the Illumina BeadStudio software. Samples with a call rate below 97 % , potentially mixed samples with excess autosomal heterozygosity or gender discrepancy (based on the sex chromosomes genotypes), and ethnic outliers (based on principal components analysis of genotypic data), were excluded from the analysis using the quality control algorithm implemented in the R package GenABEL1. Imputation of allele dosage for over 2 million SNPs on the 22 autosomal chromosomes with reference to HapMap CEU build 36 release 22 was performed using the software MACH v1.0.15 after exclusion of SNP with MAF < 0.01, call rate < 98% and HWE deviation p< 10-6.

**Analysis.** CCT measures were transformed into Z-scores for the association analysis (calculated by adjusting CCT measures for age and the three first principal components of ancestry and standardizing residuals using the ztransform command in GenABEL[4]). The ancestry principal components were obtained following multidimentional scaling of identity by state distances using the ibs and mds functions in GenABEL.
Genome-wide association analysis was performed using a mixed linear model as implemented in the probABEL[5] package using the imputed SNP allele doses as an additive fixed effect and correcting for family relatedness using the polygenic[6] and mmscore[7] 4 functions implemented in GenABEL and probABEL.
**URLs**: http://mga.bionet.nsc.ru/~yurii/ABEL/

### *Rotterdam study:*

**Datasets/Samples.** The Rotterdam Study I (RS-I) is a prospective population-based cohort study of 7983 residents aged 55 years and older living in Ommoord, a suburb of Rotterdam, the Netherlands[8]. Baseline examinations for the ophthalmic part took place between 1991 and 1993; follow-up examinations were performed from 1997 to 1999, from 2002 to 2006, and from 2009 (on going). The RS-II is another prospective population-based cohort study of 3011 residents aged 55 years and older. The rationale and study design are similar to those of the RS-I[8]. The baseline examinations of RS-II took place between 2000 and 2002; follow-up examinations were performed from 2004 to 2005 and from 2009 (ongoing). The present study included only participants with valid central corneal thickness (CCT) and genotype data.
All measurements in these studies were conducted after the Medical Ethics Committee of the Erasmus University had approved the study protocols and all participants had given a written informed consent in accordance with the Declaration of Helsinki.

**Phenotypes.** CCT measurements in the RS cohorts were done in a subset of participants. In RS-I, a total of 872 participants underwent CCT measurement, of which 200 were measured at baseline using ultrasound pachymetry (Allergan Humphrey 850, Carl Zeiss Meditec, Dublin, CA, USA)[9] and 672 at the third follow-up using non-contact biometer (Lenstar LS900, Haag-Streit, Köniz, Switzerland; see further). In RS-II, a total of 683 participants underwent CCT measurement using non-contact biometer.

**Genotyping & Imputation.** In the RS-I and RS-II cohorts, DNA was genotyped by using the Illumina Infinium II HumanHap550chip v3.0 array according to the manufacturer's protocols. Genotype data were imputed using HapMap CEU as a reference population, resulting in over 2.5 million single nucleotide polymorphisms (SNPs). Extensive quality control analyses have been performed in each cohort. Participants with low-quality DNA were excluded. Details are described elsewhere[10,11].

**Analysis.** CCT from a random eye was used in the analysis if the values from both eyes were available. Within each study, linear regression models were used to examine the associations between SNPs and CCT adjusted for age and gender. The CCTs of a total of 102 participants of RS-I were assessed using both methods (ultrasound pachymetry in 1994 and non-contact biometer in 2009). The difference in time between both measurements was approximately 15 years. Although the CCT is constant over time and the correlation between both methods around 0.9, there was a systematic difference between both measurements (data not shown). In RS-I we therefore additionally adjusted for the method used for CCT measurement. All statistical analyses were performed using SPSS version 15.0.0 for Windows (SPSS inc., Chicago, IL, USA; 2006) and GRIMP[12].

### *Western Australia RAINE study:*

**Datasets/Samples.** Recruitment of the Western Australian Pregnancy (Raine) cohort has previously been described in detail[13-15]. In brief, between 1989 and 1991 2,900 pregnant women were recruited prior to 18-weeks gestation into a randomised controlled trial to evaluate the effects of repeated ultrasound in pregnancy. Children have been comprehensively phenotyped from birth to 21 years of age (average ages of one, two, three, six, eight, ten, fourteen, seventeen and twenty-one) by trained members the Raine research team. Most of the children are of Caucasian ethnicity. Data collection included questionnaires completed by the child's primary carer and by the adolescent from age 14, physical assessments by trained assessors at all follow up years, DNA collection from year 14 follow-up. The study was conducted with appropriate institutional ethics approval, and written informed consent was obtained from all mothers.

**Phenotypes**. CCT was obtained from the Pupil Center Pachymetry readout obtained by anterior segment tomography of each dilated eye taken with an Oculus Pentacam (Optikgerate GmbH, Wetzlar, Germany).

**Genotyping & Imputation.** Study individual genotype data was extracted from the genome-wide Illumina 660 Quad Array. Any pair of individuals who were related with a $\pi > 0.1875$ (in between second and third degree relatives – e.g. between half-sibs and cousins) was investigated and the individual with the higher proportion of missing data was excluded from the 'clean' dataset (68 individuals excluded). Individuals who have low genotyping success (i.e. have lots of missing data) were excluded from the 'clean' dataset – a threshold of missingness > 3% was used for exclusion (16 individuals excluded). Additionally, if they had high levels of heterozygosity then they were also excluded (heterozygosity < 0.30 excluded 3 individual) as this may indicate sample contamination. In terms of genotyping success rates, we also excluded some SNPs if not satisfying: Hardy-Weinburg equilibrium p-value must be > $5.7 \times 10^{-7}$ (919 markers); call rate must be >95% (97,718 markers); minor allele frequency must be >0.01 (1%) (119,246 markers – includes CNV's). We have calculated the first five principal components which should be used in all GWAS analyses (at least the first two) to account for population stratification. These principal components were calculated using a subset of 42,888 SNPS that are not in LD with each other in the EIGENSTRAT package.

The MACH v1.0.16 (http://www.sph.umich.edu/csg/yli/mach/index.html) software was used for GWAS imputation on the 22 autosomes. Once the data was cleaned, a two step process was carried out using the CEU samples from HapMap phase2 build 36 release 22 as a reference panel:

**Analysis.** Individual's mean CCT from each eye was used for analysis. With PLINK as an interface with R, a linear regression model was utilized to examine the association between SNPs and CCT adjusted for age, gender and the first two principal components, which account for population stratification in this cohort.

### *DeCODE study:*

**Datasets/Samples.** The sample set from deCode consists of 708 individuals with CCT measurements, 409 clinically diagnosed glaucoma cases and 299 individuals without glaucoma from the Reykjavik Eye Study[16]. The glaucoma cases included 195 males and 214 females with mean age of 74.9 (SD 9.9), and the individuals from the Reykjavik Eye Study included 123 males and 176 females with a mean age of 69.0 (SD 9.0).

**Phenotypes.** Two systems were used to ascertain central corneal thickness. The Reykjavik Eye Study used scheimpflug slit images of the cornea documented with the Nidek EAS 1000 automated eye analysis system (Nidek EAS 1000, Gamagori, Japan). This method has been found to be comparable to ultrasound pachometry[17]. The cases collected in clinical practices used Pachscan 300p, sonomed Inc. USA ultrasound. The mean CCT values were 536 (SD 42) and 543 (SD 43) for the glaucoma cases and the non-glaucoma cases, respectively.

**Genotyping & Imputation.** All samples were typed with the Illumina HumanHap300 or HumanHapCNV370 bead chips and only samples with more than 98% genotype yield were included in the analysis. After quality filtering, 290,350 SNPs were used to impute genotypes for additional 2,164,323 ungenotyped SNPs using the IMPUTE software[18] and 114 phased haplotypes for the HapMap CEU samples (version 22) as a training set.

**Analysis.** The analysis was done using the SNPTEST (version 2.1.1) software, assuming an additive model for the genetic effect by regressing the CCT values on the expected genotype counts adjusting for age and sex by including them as covariates in the analysis. A likelihood score test (the -method score option in SNPTEST) was used to take the genotype uncertainty into account. The glaucoma cases and the individuals without glaucoma were analyzed separately and the P-values were adjusted for relatedness of the individuals by dividing the corresponding $\chi^2$ statistic by 1.020 and 1.017 for the analysis of glaucoma and non-glaucoma cases, respectively.

### *Gutenberg Health Study:*

**Datasets/Samples.** The Gutenberg Health Study (GHS) is a population-based, prospective, observational cohort study in the Rhine-Main Region in midwestern Germany with a total of about 15000 participants and follow-up after five years. The study sample is recruited from subjects aged between 35 and 74 years at the time of the exam. The sample was drawn randomly from local governmental registry offices and stratified by gender, residence (urban and rural) and decade of age. Exclusion criteria were insufficient knowledge of the German language to understand explanations and instructions, and physical or psychic inability to participate in the examinations in the study center. Individuals were invited for a 5-hour baseline-examination to the study center where clinical examinations and collection of blood samples were performed. An important feature of the study design is the interdisciplinary combination of an ophthalmological examination, general and especially cardiovascular examinations, psychosomatic evaluation, laboratory tests, and biobanking for proteomic and genetic analyses.

**Phenotypes.** All participants underwent an ophthalmological investigation of 25 minutes' duration taking place between 11:00 a.m. and 8:00 p.m. This examination was based on standard operating procedures and included a medical history of eye diseases, autorefraction and visual acuity testing (Humphrey® Automated Refractor/Keratometer (HARK) 599™, Carl Zeiss Meditec AG, Jena, Germany), visual field screening using frequency doubling technology (Humphrey® Matrix

Perimeter, Carl Zeiss Meditec AG, Jena, Germany), central corneal thickness and keratometry measurement (Scheimpflug imaging with the Pachycam™, Oculus, Wetzlar, Germany), slitlamp biomicroscopy with undilated pupils (Haag-Streit BM 900®, Bern, Switzerland) and non-mydriatic fundus photography (Visucam PRO NM,™, Carl Zeiss Meditec AG, Jena, Germany), all administered by an ophthalmologist. IOP was measured with a non-contact tonometer and automatic airpuff control (Nidek NT-2000™, Nidek Co., Japan). The study was approved by the Medical Ethics Committee of the University Medical Center Mainz and by the local and federal data safety commissioners. According to the tenets of the Declaration of Helsinki, written informed consent was obtained from all participants prior to entering the study.

**Genotyping & Imputation.** Within GHS, DNA was extracted from buffy-coats from EDTA blood samples as described in Zeller et al[19].Genotyping was performed on 3,463 individuals in 2008 (GHS I) and another 1,439 individuals in 2009 (GHS II) using the Affymetrix Genome-Wide Human SNP 6.0 Array. DNA samples using the Affymetrix Genome-Wide Human SNP Nsp/Sty Assay 5.0 and hybridization were processed in accordance with the manufactures' standard recommendations. Genotyped individuals were of European descent only.
Genotypes were determined using the Birdseed v2 calling algorithm. Only samples with a contrast QC≥0.4 were included in the final genotype calling. Quality control on sample level comprised exclusion of samples with a call rate ≤97%, deviation from expected heterozygosity by more than three standard deviations, and relatedness based on identity by state distance measures. On the marker level we excluded polymorphisms with a call rate ≤98% in cases or controls, minor allele frequency ≤0.01 and deviation from Hardy-Weinberg equilibrium (P≤0.0001). Cluster plots were inspected for all markers with P<0.001 in the GWA analysis. After quality control, 2,996 individuals for GHS I and 1,179 individuals for GHS II remained for further analyses. Imputation was performed using Impute (v2.1.0) software (http://mathgen.stats.ox.ac.uk/impute/impute.html) according to the CEU HapMap 2 release 22 (build 36) reference dataset. Imputed genotypes were analyzed using the SNPTEST software taking genotype uncertainty into account (https://mathgen.stats.ox.ac.uk/genetics_software/snptest/snptest.html).

**Analysis.** Linear regression models with a 1 degree of freedom trend test were used to examine the associations between SNPs and CCT, adjusted for age and gender. We calculated regression coefficients using these linear regression models. The analysis was performed using PLINK software assuming an additive model.

### *Singapore studies (Vithana et al (2011)[20] and Cornes et al (2012)[21]):*

**Datasets/Samples.**
The sample collections enrolled in Singapore have been previously described[20,21]. The enrollment of all sample collections adhered to the Declaration of Helsinki. Ethics approval was obtained from the Singapore Eye Research Institute (SERI) Institutional Review Board (IRB). All participants were given a choice to provide written, informed consent in English, Malay, Mandarin, or using bilingual interviewers. Both versions of study information sheet and informed consent form were approved by the SERI IRB before the study commenced.
SiMES is a population-based, cross-sectional study of 3280 Malay adults aged from 40 to 79 years. Details of the SiMES design, sampling plan, and methods have been reported elsewhere[22]. In brief, an age-stratified random sampling of all Malay adults, aged 40 to 80 years, residing in 15 residential districts in the south- western part of Singapore was drawn from the computer-generated random list of 16,069 Malay names provided by the Ministry of Home Affairs. A total of 1400 names from each decade of age (40-49, 50-59, 60-69, and 70-79 years), or 5600 names, were selected. Of these, 4168 individuals (74.4%) were determined to be eligible to participate. A person was considered ineligible if he or she had moved from the residential address, had not lived there in the past 6 months, was deceased, or was terminally ill. Of the 4168 eligible individuals, 3280 participants (78.7%) took part in the study. The study was conducted from August 2004 through to June 2006.
The SICC is designed to complement the SiMES in ethnic Indians and ethnic Chinese residents of Singapore. This study was further divided into the Singapore Indian Eye Study (SINDI) and Singapore Chinese Eye Study (SCES). Further information about the SICC has been published

elsewhere[23]. Similar to SiMES, the SINDI study is a population-based, cross-sectional epidemiological study, but of ethnic Indian adults aged between 40 and 80+ years residing in Singapore. As with SiMES, the Ministry of Home Affairs provided an initial computer-generated list of 12,000 ethnic Indian names derived from a simple random sampling of all ethnic Indian adults aged 40-80+ years of age residing in 15 residential districts in South-Western Singapore. From this list, a final sampling frame of 6,350 ethnic Indian residents was derived using an age-stratified random sampling strategy. SINDI was conducted from March 2007 to May 2007 and recruited 3,400 (75% response rate) participants.
SCES: In similar vein to SiMES and SINDI, the Singapore Chinese Eye Study (SCES) is a population-based, cross-sectional study of Chinese adults residing in the south- western part of Singapore. The Ministry of Home Affairs provided an initial computer-generated list ethnic Chinese names of adults aged 40-80+ years of age. A final sampling frame of 6,350 ethnic Chinese residents was derived from this list using an age-stratified random sampling strategy similar to SiMES and SINDI. The ongoing SCES began in February, 2009 with an aim to recruit 3,300 (75% response rate) participants[23]. As of June 2011, we recruited and genotyped 1,952 participants, which was used in this analyses.

**Phenotypes.**
SiMES, SINDI, SCES: Five CCT measurements were obtained from each eye with an ultrasound pachymeter (Advent, Mentor O & O, Norwell, MA) and the median reading was taken[24,25]. As there was good correlation between the measurements in both eyes, only the readings from the right eye were used for analysis.

**Genotyping and Imputation.**
DNA was extracted from blood samples drawn from enrolled participants using standard laboratory techniques. Genome-wide genotyping of SINDI, SiMES and SCES was performed using the Illumina 610K Beadchip, as per manufacturer's specifications.
The imputation for the three Asian sample sets was undertaken using the imputation software IMPUTE. The HapMap Phase II JPT+CHB set was used as reference panel for the Chinese samples, and Phase III cosmopolitan panel (multi-ethnic) was used for the Indian and Malaysian samples. Stringent QC on imputation quality was applied (INFO>0.90). The numbers of imputed SNPs after QC were ~1.8 million for Chinese set and ~1 million for Indian or Malays.

**Analysis.**
Single cohort and meta-analysis of SINDI, SiMES, and SCES has been previously described[21]. For SINDI, 2516 samples passing quality checks had complete data for CCT measurements, age, and gender. For SiMES, 2514 samples passing quality checks had complete data for CCT measurements, age, and gender. For SCES, a final number of 1,883 individuals with complete data for CCT measurements, age and gender were available for analysis. We measured the association between SNP genotypes and CCT using linear regression modeling for genotype trend effects adjusted for age and gender. Further adjustment by incorporating the top principal components (PCs) of genetic stratification (PC1 to PC3 for SINDI, and PC1 plus PC2 for SiMES and SCES) was performed to minimize the effects of population stratification as previously described[20,21].

### *ANZRAG study (Burdon et al (2011)[26]):*
**Datasets/Samples.** Patients resident in Australia or New Zealand with advanced glaucoma were referred to the Australian and New Zealand Registry of Advanced Glaucoma by their treating ophthalmologist.

**Phenotypes.** All participants met the Registry's definition of advanced primary open angle glaucoma. Briefly, this was defined as best-corrected visual acuity worse than 6/60 due to POAG, or a reliable 24-2 Visual Field with a mean deviation of worse than -22db or at least 2 out of 4 central fixation squares affected with a Pattern Standard Deviation of < 0.5%. The field loss must be due to OAG, and the less severely affected eye was also required to have signs of glaucomatous disc damage. Secondary glaucoma and patients with mutations in *MYOC* were excluded. DNA was extracted from peripheral whole blood.

**Genotyping & Imputation.** 615 ANZRAG participants were genotyped on Illumina Human1M-Omni arrays. SNPs with a mean BeadStudio GenCall score <0.7 were excluded from the controls. All samples had successful genotypes for >95% of SNPs. SNPs with call rates either <0.95 (minor allele frequency (MAF) > 0.05) or <0.99 (MAF > 0.01), Hardy-Weinberg equilibrium in controls P < 10.6 and/or MAF < 0.01 were excluded. Ancestry outliers were identified by principal component (PC) analysis using data from 11 populations of the HapMap 3 and 5 Northern European populations genotyped by the GenomeEUtwin consortium using the EIGENSOFT package and a subset of 160,000 independent SNPs. Twenty-five Individuals lying 2 standard deviations from the mean PC1 and PC2 scores were removed.. The imputation was undertaken with reference to 1000 Genome Pilot 1 (June 2010 version) using MACH. SNPs with small MAF (MAF<0.01) and low imputation quality ($R^2$ <0.3) were discarded in the QC.

**Analysis.** 363 participants had CCT data available and were used in this analysis. The association analysis was run in PLINK adjusting for age and sex.

### *GLAUGEN study:*

**Datasets/Samples.** 976 cases and 1,140 controls collected from three study sites [Nurses Health study, Health Professionals Follow-up Study and the Genetic Etiologies of Primary-Open angle Glaucoma Study (GEP)] were genotyped for the GLAUGEN study. All cases and controls were residents of the continental United States and were of mainly European ancestry, which was confirmed by both self-identification and genetic markers. All individuals included in the GLAUGEN CCT analysis were POAG cases collected from the Massachusetts Eye and Ear Infirmary.

**Phenotypes.** We observed a strong correlation between the right eye CCT and left eye CCT (R2=0.92) in the GLAUGEN study population. Therefore, we used the average CCT in the final analysis. We removed 10 outliers which are defined by large left-right differences (beyond 2.5 standard deviation of the overall distribution of left-right differences). A lack of left/right eye correlation may be due to true difference between the eyes, measurement artefacts, or unknown corneal defects.

**Genotyping & Imputation.** Genotyping was performed using the Illumina Human660W_Quad_v1 array and 495,132 SNPs passed quality control filters. Illumina's BeadStudio and GenomeStudio and Autocall software along with genotype cluster definitions based on study samples were used to generate genotyping calls. SNPs with a GenTrain score <0.6, cluster separation score <0.4 and call rate <97% were considered technical failures at the genotyping center and were automatically deleted before release for further quality control. Subsequent data quality control measures consisted of identifying and removing samples with gender misidentification, unexpected duplicates and unexpected relatedness. Analysis of connectivity removed samples that appeared to be related to other samples and/or suggestive of contamination. Any SNP with missing call rate >2% or with Hardy Weinberg p-value < 10-4 in the control population was excluded.

**Analysis.** We checked for population substructure using principal components analysis performed in Eigensoft. We identified 10 individuals as population outliers based on PCA results, four were self-reported Hispanic ethnicity. The ten PCA outliers were removed from the analysis and all remaining individuals were Caucasian. Linear regression was done using PLINK v1.07, included age and gender as covariates.

### *NEIGHBOR study:*

**Datasets/Samples.** 2,170 cases and 2,347 controls collected from 12 sites throughout the United States were genotyped for the NEIGHBOR study. CCT data was available for individuals from all sites except for the University of California, San Diego and Stanford University. All cases and controls were residents of the continental United States and were of mainly European ancestry, which was confirmed by both self-identification and genetic markers.

**Phenotypes.** We observed a strong correlation between right eye CCT and left eye CCT (R2=0.83) in our sample, so we used the mean CCT as our primary analysis outcome. We removed 16 outliers which are defined by large left-right differences (beyond 2.5 standard deviation of the overall distribution of left-right differences) and 1 individual with an extremely small average CCT value (<374 microns). Additionally, we removed individuals with known corneal disease or known non-Caucasian ancestry.

**Genotyping & Imputation.** Genotyping was performed using the Illumina Human660W_Quad_v1 array and 523,528 SNPs passed quality control filters. Allele cluster definitions for each SNP were determined using Illumina GenomeStudio Genotyping Module version 1.7.4, GenTrain version 1.0 and the combined intensity data from 99.9% of the samples. The resulting cluster definitions were used on all samples. Genotypes were not called if the quality threshold (Gencall score) was below 0.15. Genotypes were released by CIDR for 557,029 SNPs (99.58% of attempted). Genotypes were not released for SNPs that had call rates less than 85%, more than 1 HapMap replicate error, cluster separation less than 0.2, more than a 3% (autosomal) or 2.2% (X chromosome) difference in call rate between genders, more than 0.4% (X chromosome) male heterozygosity, or more than a 8% (autosomal) difference in AB frequency.

**Analysis.** We checked for population substructure using principal components analysis as implemented by EIGENSTRAT. After examining the top 10 PCs, we determined that the sample is a reasonably homogeneous population. Using a t-test, we compared the mean CCT between POAG cases and controls. We also found the instrument used to measure CCT (DGH Technology, Inc. ultrasound table unit versus portable handheld) had a significant effect on mean CCT (P-value<.001). Therefore, we included measurement device as covariates in the final model, along with age and gender. We performed linear regression using PLINK v1.07 for POAG cases and controls respectively.

### *UK South Hampton study:*

**Datasets/Samples.** Four hundred (400) primary open angle patients from a cohort of patients being recruited in Hampshire (UK) were included in this study. Patients were recruited following the tenets of the declaration of Helsinki, informed consent was obtained and the research was approved by the Southampton & South West Hampshire Research Ethics Committee. Patients were all diagnosed as POAG cases and further defined as normal tension glaucoma (NTG) if the average IOP over both eyes ≤21 mmHg, and high tension glaucoma (HTG) if otherwise. All showed visual field loss in at least one eye. A full description of the cohort is given elsewhere[27]. Cases diagnosed as psuedoexfoliation glaucoma and those with a known myocilin mutation were excluded.

**Phenotypes.** CCT information was available on 191 cases and 47 controls in this study. Cases were unrelated and of Caucasian ethnicity.

**Genotyping & Imputation.** Primary open angle glaucoma patients (n=400) were genotyped on the Affymetrix SNP 6.0 array. Standard QC filtering followed, removing SNPs with MAF<5% and HWE p<0.001 (tested in controls but removed from cases and controls) and SNPs or samples with a high degree of missingness >10%. The HWE test (in controls) is generally used to control for genotyping error when cases and controls are genotyped together. However as the cases were genotyped separately extra QC steps were carried out. Firstly, the average confidence score for the genotypes (from the Affymetrix SNP calling software "Genotyping console") were calculated for each SNP across individuals and SNPs with confidence scores which fell two standard deviations above the mean (worse confidence) were removed. We also removed SNPs with extreme deviations from HWE (p<1x10-10) in cases. 681,552 SNPs were available for analysis after QC.

**Analysis.** A linear regression was carried out in PLINK for cases and controls separately using the average CCT over both eyes as the quantitative trait. Due to its relatively small sample size, the control set was not utilised in this meta-analysis.

### *Hong Kong cohort of normal tension glaucoma patients:*

**Datasets/Samples.** Patients with normal tension glaucoma (NTG) were recruited from the eye clinics of the Hong Kong Eye Hospital and the Prince of Wales Hospital, Hong Kong. Diagnosis of NTG was made after complete ophthalmic examinations and according to the following criteria: (1) no primary pathologies for glaucoma, e.g., trauma, uveitis, steroid-induced, exfoliation glaucoma, or neovascular glaucoma; (2) open anterior chamber angle, with Shaffer Grade 2 or above in dark room gonioscopy, without indentation; (3) evidence of characteristic glaucomatous optic disc changes including narrowing of the neuroretinal rim and/or thinning of the retinal nerve fiber layer; (4) fulfilling Anderson's criteria for minimal abnormality in glaucomatous visual field; and (5) highest recorded intraocular pressure below 21 mmHg. A total of 198 unrelated NTG patients were recruited, with all being Han Chinese. The mean (SD) age of study subjects was 64.1 (12.8) years. The female to male ratio was 1.02 (100/98). All patients have no other major eye diseases.
The study protocol was approved by the Ethics Committee on Human Research of the Chinese University of Hong Kong. Informed consents were obtained from all study subjects. All procedures were conducted in accordance with the tenets of the Declaration of Helsinki.

**Phenotypes.** Central corneal thickness (CCT) was measured for both eyes using a TOMEY SP 3000 ultrasonic pachymeter (Tomey Corp., Nagoya, Japan). CCT in the both eyes followed normal distribution (P=0.80 and 0.29 in one-sample K-S test). The mean (SD) CCT was 536.0 (34.6) μm in the right eye and 537.2 (35.0) μm in the left eye. Since the CCT in the both eyes were highly correlated (Pearson correlation coefficient = 0.96, $P=3.7x10^{-112}$) and were not significantly different between eyes (P=0.21, Student's t-test), the mean CCT value of both eyes was used throughout as our analysis. Mean value of the CCT was 536.9 (34.5) μm.

**Genotyping & Imputation.** The samples were genotyped on the Illumina CNV370Quad arrays at deCODE genetics, Iceland. SNPs on the X and Y chromosomes as well as the copy number variant (CNV) probes were removed from further analysis. A total of 1323 SNPs with call rates <95% were eliminated from the analysis. 37640 SNPs were also excluded as they had a minor allele frequency (MAF) < 1% and another 331 were excluded because of a significant deviation from Hardy-Weinberg Equilibrium (HWE) ($p<10^{-4}$). After these steps, the number of individuals available with CCT measures and genotypes was 198 and the number of markers was 293,957. We examined potential genetic relatedness on the basis of pairwise identity by state for all the successfully genotyped samples by using PLINK 1.07 software. No relatedness was found. Potential population stratification was tested using the genomic control algorithm in PLINK. The genomic inflation factor (based on median chi-squared) was 1.0, suggesting a high degree of homogeneity of the study sample.

**Analysis. .** A linear regression was carried out in PLINK v1.07 for the 198 NTG patients using the mean value of the CCT over both eyes as the quantitative trait.

### *USA keratoconus study[28]*:

**Samples.** Clinically affected Caucasian keratoconus cases (N=240) were enrolled into the GWAS as a part of the longitudinal videokeratography and genetic study at the Cornea Genetic Eye Institute[29]. After removing samples with poor quality of genotyping, 222 samples were included in the analysis. Caucasian controls (N=3324) were obtained from the Cardiovascular Health Study (CHS), a population-based cohort study of risk factors for cardiovascular disease and stroke in adults 65 years of age or older, recruited at four field centers[30,31]. 5,201 predominantly Caucasian individuals were recruited in 1989-1990 from random samples of Medicare eligibility lists, followed by an additional 687 African-Americans recruited in 1992-1993 (total n= 5,888). CHS was approved by the Institutional Review Board at each recruitment site, and subjects provided informed consent for the use of their genetic information. African-American CHS participants were excluded from analysis due to insufficient number of ethnically-matched cases.

**Methods.** IMPUTE version 2.1.0[18] was used to perform imputation of the genotyping data of SNPs rs1324183 and rs9938149 in keratoconus patients and CHS Caucasian controls using HapMap Phase I and II data (release #22 , NCBI Build 36) as the reference panel. Linkage disequilibrium

between lead SNPs and their proxies was calculated by a web-based computer tool SNAP using Caucasian panel[32].

### *Australian and Northern Ireland Keratoconus*

**Datasets/Samples.** Australian participants with keratoconus (n=517) were ascertained through the Department of Ophthalmology of Flinders Medical Centre, Adelaide, Australia; private optometry practices in Adelaide and Melbourne, Australia; the Royal Victorian Eye and Ear Hosptial, Melbourne, Australia; and by Australia-wide mail out to members of Keratoconus Australia, a community-based support group for patients. Patients from Northern Ireland (n=135) were recruited from the Ophthalmology Department of the Belfast Health and Social Care National Health System Trust. Clinical data were obtained from the participants' eye care practitioner, and patients were included in the study only if they met the recruitment criteria. The Blue Mountains Eye Study was used as the control cohort. This population study of individuals over the age of 50 years living in the Blue Mountains area west of Sydney undertook detailed ophthalmic evaluations of all participants. 2761 participants had genotyping information available.

**Phenotypes.** The diagnosis of keratoconus was based on clinical examination and videokeratography pattern analysis. Clinical examination included slit lamp biomicroscopy, cycloplegic retinoscopy, and fundus evaluations. Slit lamp biomicroscopy was used to identify stromal corneal thinning, Vogt's striae, or a Fleischer ring. A retinoscopic examination was performed with a fully dilated pupil to determine the presence or absence of retroillumination signs of keratoconus, such as the oil droplet sign and scissoring of the red reflex. Videokeratography evaluation was performed on each eye by topographic modeling. Patients were considered as having keratoconus if they had at least one clinical sign of the disease and by confirmatory videokeratography map with an asymmetric bowtie pattern with skewed radial axis above and below the horizontal meridian (AB/SRAX). A history of penetrating keratoplasty performed because of keratoconus was also sufficient for inclusion.

**Genotyping.** Cases were genotyped in 2 plexes on a Sequenom Mass Array (Sequenom Inc) using iPlex gold chemistry (Sequenom Inc) at the Australian Genome Research Facility, Brisbane Australia. Four SNPs failed genotyping and were thus excluded from the analysis. Controls (Blue Mountains Eye Study) were genotyped on Illumina HumanHap 610 Arrays by the Wellcome Trust Case Control Consortium 2. Data relating to the genotyped SNPs were extracted for 2761 genotyped samples and merged with the case data.

**Analysis.** SNPs were assessed for allelic association in PLINK.

### *Disease diagnostic criteria*

The diagnosis of keratoconus for Australia and Northern Ireland cases was based on clinical examination and videokeratography pattern analysis. Clinical examination included slit lamp biomicroscopy, cycloplegic retinoscopy, and fundus evaluations. Slit lamp biomicroscopy was used to identify stromal corneal thinning, Vogt's striae, or a Fleischer ring. A retinoscopic examination was performed with a fully dilated pupil to determine the presence or absence of retroillumination signs of keratoconus, such as the oil droplet sign and scissoring of the red reflex. Videokeratography evaluation was performed on each eye by topographic modeling. Patients were considered as having keratoconus if they had at least one clinical sign of the disease and by confirmatory videokeratography map with an asymmetric bowtie pattern with skewed radial axis above and below the horizontal meridian (AB/SRAX). A history of penetrating keratoplasty performed because of keratoconus was also sufficient for inclusion. Similar diagnostic criteria were used in the US study, as previously described[28].

The POAG cases were defined in the GLAUGEN and NEIGHBOR studies as individuals for whom reliable visual field (VF) tests show characteristic VF defects consistent with glaucomatous

optic neuropathy. Individuals were classified as affected if the VF defects were reproduced on a subsequent test or if a single qualifying VF was accompanied by a cup-disc ratio (CDR) of 0.7 or more in at least one eye. The examination of the ocular anterior segment did not show signs of secondary causes for elevated IOP such as exfoliation syndrome or pigment dispersion syndrome and the filtration structures were deemed to be open based on clinical measures. Elevation of IOP was not a criterion for inclusion; however, 67% of cases did have a history of elevated IOP (≥22 mm Hg) measured in a clinical setting (typically between the hours of 8AM and 5PM) and were classified as high-pressure glaucoma (HPG). Cases with IOP <22 mm Hg measured in the clinic at the time of study enrollment (without treatment) were classified as normal-pressure glaucoma (NPG). Cases undergoing IOP-lowering therapy at the time of enrollment were included in the HPG group if they had a documented history of IOP >22 prior to treatment and cases undergoing IOP-lowering therapy at the time of enrollment were included in the NPG if they did not have recorded pressures >22 mmHg before treatment. As glaucoma patients are long-term patients with several clinic visits each year, for most of the glaucoma cases in this study the IOP measurements were made at least twice on multiple occasions. Controls had normal optic nerves (cup-disc ratios ≤0.6) and normal intraocular pressure (≤21 mm Hg)[33].

Enrolment in the advanced OAG category of ANZRAG was defined by severe visual loss resulting from OAG[26]. This includes best-corrected visual acuity worse than 6/60 due to OAG, or a reliable 24-2 Visual Field with a mean deviation of worse than -22db or at least 2 out of 4 central fixation squares affected with a Pattern Standard Deviation of < 0.5%. The field loss must be due to OAG, and the less severely affected eye was also required to have signs of glaucomatous disc damage. Clinical exclusion criteria for this study included: i) pseudoexfoliation or pigmentary glaucoma, ii) angle closure or mixed mechanism glaucoma, iii) secondary glaucoma due to aphakia, rubella, rubeosis or inflammation, iv) infantile glaucoma, v) glaucoma in the presence of a known associated syndrome, vi) mutation in the MYOC gene (by direct sequencing of exon 3). Identical criteria were applied to GIST participants to select equivalent advanced glaucoma cases. The controls were not screened for glaucoma and hence will include some present (or future) glaucoma cases. Although this slightly reduces power to test for association relative to screened controls, given the low prevalence of advanced glaucoma (~ 3/1000), the reduction in power is likely to be small.

## Reference


1. Pruim, R.J. et al. LocusZoom: regional visualization of genome-wide association scan results. *Bioinformatics* **26**, 2336-7 (2010).
2. Lu, Y. et al. Common genetic variants near the Brittle Cornea Syndrome locus ZNF469 influence the blinding disease risk factor central corneal thickness. *PLoS Genet* **6**, e1000947 (2010).
3. Vitart, V. et al. New loci associated with central cornea thickness include COL5A1, AKAP13 and AVGR8. *Hum Mol Genet* **19**, 4304-11 (2010).
4. Aulchenko, Y.S., Ripke, S., Isaacs, A. & van Duijn, C.M. GenABEL: an R library for genome-wide association analysis. *Bioinformatics* **23**, 1294-6 (2007).
5. Aulchenko, Y.S., Struchalin, M.V. & van Duijn, C.M. ProbABEL package for genome-wide association analysis of imputed data. *BMC Bioinformatics* **11**, 134 (2010).
6. Thompson, E.A. & Shaw, R.G. Pedigree analysis for quantitative traits: variance components without matrix inversion. *Biometrics* **46**, 399-413 (1990).
7. Chen, W.M. & Abecasis, G.R. Family-based association tests for genomewide association scans. *Am J Hum Genet* **81**, 913-26 (2007).
8. Hofman, A. et al. The Rotterdam Study: 2010 objectives and design update. *Eur J Epidemiol* **24**, 553-72 (2009).
9. Wolfs, R.C. et al. Distribution of central corneal thickness and its association with intraocular pressure: The Rotterdam Study. *Am J Ophthalmol* **123**, 767-72 (1997).
10. Ramdas, W.D. et al. Genetic architecture of open angle glaucoma and related determinants. *J Med Genet* **48**, 190-6 (2011).
11. Rivadeneira, F. et al. Twenty bone-mineral-density loci identified by large-scale meta-analysis of genome-wide association studies. *Nat Genet* **41**, 1199-206 (2009).
12. Estrada, K. et al. GRIMP: a web- and grid-based tool for high-speed analysis of large-scale genome-wide association using imputed data. *Bioinformatics* **25**, 2750-2 (2009).
13. Evans, S., Newnham, J., MacDonald, W. & Hall, C. Characterisation of the possible effect on birthweight following frequent prenatal ultrasound examinations. *Early Hum Dev* **45**, 203-14 (1996).
14. Newnham, J.P., Evans, S.F., Michael, C.A., Stanley, F.J. & Landau, L.I. Effects of frequent ultrasound during pregnancy: a randomised controlled trial. *Lancet* **342**, 887-91 (1993).
15. Williams, L.A., Evans, S.F. & Newnham, J.P. Prospective cohort study of factors influencing the relative weights of the placenta and the newborn infant. *BMJ* **314**, 1864-8 (1997).
16. Jonasson, F. et al. Prevalence of open-angle glaucoma in Iceland: Reykjavik Eye Study. *Eye (Lond)* **17**, 747-53 (2003).
17. Sakamoto, Y. & Sasaki, K. Accuracy of biometrical data obtained from Nidek EAS 1000. *Ophthalm Res* **26**, 26-32 (1994).
18. Marchini, J., Howie, B., Myers, S., McVean, G. & Donnelly, P. A new multipoint method for genome-wide association studies by imputation of genotypes. *Nat Genet* **39**, 906-13 (2007).
19. Zeller, T. et al. Genetics and beyond--the transcriptome of human monocytes and disease susceptibility. *PLoS One* **5**, e10693 (2010).
20. Vithana, E.N. et al. Collagen-related genes influence the glaucoma risk factor, central corneal thickness. *Hum Mol Genet* **20**, 649-58 (2011).
21. Cornes, B.K. et al. Identification of four novel variants that influence central corneal thickness in multi-ethnic Asian populations. *Hum Mol Genet* **21**, 437-45 (2012).
22. Foong, A.W. et al. Rationale and methodology for a population-based study of eye diseases in Malay people: The Singapore Malay eye study (SiMES). *Ophthalmic Epidemiol* **14**, 25-35 (2007).
23. Lavanya, R. et al. Methodology of the Singapore Indian Chinese Cohort (SICC) eye study: quantifying ethnic variations in the epidemiology of eye diseases in Asians. *Ophthalmic Epidemiol* **16**, 325-36 (2009).
24. Su, D.H. et al. Central corneal thickness and its associations with ocular and systemic factors: the Singapore Malay Eye Study. *Am J Ophthalmol* **147**, 709-716 e1 (2009).
25. Su, D.H. et al. Diabetes, hyperglycemia, and central corneal thickness: the Singapore Malay Eye Study. *Ophthalmology* **115**, 964-968 e1 (2008).
26. Burdon, K.P. et al. Genome-wide association study identifies susceptibility loci for open angle glaucoma at TMCO1 and CDKN2B-AS1. *Nat Genet* **43**, 574-8 (2011).
27. Ennis, S. et al. Prevalence of myocilin gene mutations in a novel UK cohort of POAG patients. *Eye (Lond)* **24**, 328-33 (2010).
28. Li, X. et al. A genome-wide association study identifies a potential novel gene locus for keratoconus, one of the commonest causes for corneal transplantation in developed countries. *Hum Mol Genet* **21**, 421-9 (2012).
29. Wang, Y., Rabinowitz, Y.S., Rotter, J.I. & Yang, H. Genetic epidemiological study of keratoconus: evidence for major gene determination. *Am J Med Genet* **93**, 403-9 (2000).
30. Fried, L.P. et al. The Cardiovascular Health Study: design and rationale. *Ann Epidemiol* **1**, 263-76

(1991).
31. Psaty, B.M. et al. Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium: Design of prospective meta-analyses of genome-wide association studies from 5 cohorts. *Circ Cardiovasc Genet* **2**, 73-80 (2009).
32. Johnson, A.D. et al. SNAP: a web-based tool for identification and annotation of proxy SNPs using HapMap. *Bioinformatics* **24**, 2938-9 (2008).
33. Wiggs, J.L. et al. Common variants at 9p21 and 8q22 are associated with increased susceptibility to optic nerve degeneration in glaucoma. *PLoS Genet* **8**, e1002654 (2012).

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**List of NEIGHBOR Consortium Members**

R Rand Allingham MD
Department of Ophthalmology, Duke University Medical School

Don Budenz MD
Department of Ophthalmology, University of Miami Medical School

David Friedman, MD, MPH, PhD
Department of Ophthalmology, Johns Hopkins University School of Medicine

Douglas Gaasterland MD
Eye Doctors of Washington DC

Terry Gaasterland PhD
University of California, San Diego

Michael A Hauser MD
Departments of Medicine and Ophthalmology, Duke University School of Medicine

Jonathan L Haines PhD
Center for Human Genetic Research, Vanderbilt University School of Medicine

Jae Hee Kang DSc
Department of Medicine, Brigham and Women's Hospital, Harvard Medical School

Richard Lee, MD PhD
Department of Ophthalmology, University of Miami School of Medicine

Paul Lichter, MD
Department of Ophthalmology, University of Michigan School of Medicine

Stephanie Loomis
Department of Ophthalmology, Harvard Medical School

Yutao Liu, MD PhD
Department of Ophthalmology, Duke University School of Medicine

Catherine A. McCarty
Essentia Institute of Rural Health, Duluth, MN

Lana Olson
Center for Human Genetics Research, Vanderbilt University School of Medicine

Louis R Pasquale, MD
Department of Ophthalmology, Harvard Medical School

Margaret Pericak-Vance PhD
Institute for Human Genomics, University of Miami School of Medicine

Syoko Moroi MD PhD
Department of Ophthalmology, University of Michigan School of Medicine

Anthony Realini MD
Department of Ophthalmology, University of West Virginia School of Medicine

Julia E Richards PhD

Department of Ophthalmology, University of Michigan School of Medicine

Joel S Schuman MD
Department of Ophthalmology, University of Pittsburgh School of Medicine

Kuldev Singh MD
Department of Ophthalmology, Stanford University School of Medicine

Doug Vollrath MD PhD
Department of Genetics, Stanford University School of Medicine

Robert Weinreb MD
Department of Ophthalmology, University of California San Diego

Janey L Wiggs MD, PhD
Department of Ophthalmology, Harvard Medical School

Gadi Wollstein MD
Department of Ophthalmology, University of Pittsburgh

Brian L Yaspan PhD
Center for Human Genetics Research, Vanderbilt University School of Medicine

Don Zack MD, PhD
Department of Ophthalmology, Johns Hopkins University School of Medicine

Kang Zhang, MD, PhD
Department of Ophthalmology, University of California, San Diego